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EDITORIAL

# Identifying host immune effectors critical for protection against *Candida albicans* infections

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*Candida albicans* is one of the most important human fungal pathogens and can manifest as a wide variety of infections, ranging from benign superficial disease to life-threatening invasive and disseminated infection. Humans with intact immune systems are highly resistant to *C. albicans*, and in fact most fungal, infections.[1] Thus, many fungal pathogens are labeled as "opportunistic." But this label unfairly anthropomorphizes the organism and imbues it with an ulterior motive when in fact the fungi is merely responding to a change in the host's condition or physiology.[2] Neither the microbe nor the host is static, and it is clearly the dynamics that are critical for determining whether an infection develops. While many researchers define virulence only in terms of the pathogen, virulence may be better defined as "a reflection of the outcome of host-microbe interaction in a susceptible host, rather than a stable or predictable microbial trait."[3]

Therefore dissecting and elucidating the host immune effectors critical for maintaining protection against *C. albicans* infections is critical for truly understanding Candida infection pathogenesis (or virulence). For example, phagocytes are generally thought to be the most effective cellular immune effector for controlling and clearing Candida infections. Neutrophils play a critical role in innate host defense against both Candida mucosal and invasive infections.[4,5] Haematopoietic growth factors (specifically granulocyte colony-stimulating factors, G-CSF, and granulocyte-macrophage colony stimulating factor, GM-CSF) are potent drivers of phagocyte differentiation, recruitment and activation. In preclinical models, G-CSF therapy protects against lethal fungal infections[6] and augments antifungal drug activity.[7] In clinical studies, prophylactic use of GM-CSF resulted in reduced incidence of fatal infections in acute myeloid leukemia patients[8] and improved survival from fungal infections in stem cell transplant patients.[9] It is also well-established that cytokines play a key role in epithelial immunity against Candida infection. For instance, patients with chronic mucocutaneous candidiasis have severely defective Th17 responses.[10] When further exploring the Th17 response (specifically the dectin-1/CARD9/Th17 pathway), it was noted that patients with defective c-type lectin pattern recognition receptor dectin-1[11] and/or downstream adaptor CARD9[12] suffer from mucocutaneous candidiasis. Interestingly, one study showed that treatment with G-CSF in patients with isolated chronic mucocutaneous candidiasis resulted in a complete clinical remission and complete restoration of IL-17 levels[13] — although these results could not be reproduced by another group.[14] Finally, there is growing appreciation for the role that mucosal epithelial cells play in the first line defense against Candida infections. In addition to its function as a physical barrier to fungal invasion, recent evidence has revealed the critical role that epithelial cells play in triggering innate immune responses. For example, when human gingival epithelial cells are exposed to *Candida spp.*, toll-like receptors are upregulated; antimicrobial peptides (specifically $\beta$-defensins) are induced; and fungal burden is decreased.[15,16] In the gastrointestinal tract, commensal gut bacteria can induce antimicrobial peptides (namely LL-37/CRAMP via HIF-1a) to maintain *C. albicans* colonization resistance in mice, and pharmacologic activation of these gut immune effectors not only reduces *C. albicans* colonization but significantly decreases dissemination.[17] Thus, elucidating host immune effectors critical for protecting against *C. albicans* colonization or invasion not only provides critical insight into infectious disease pathogenesis but may provide the foundation for novel therapeutic strategies as well.

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In the study by Break et al.[18] in this issue of *Virulence*, the role that dendritic cells play in antifungal (specifically anti *Candida albicans*) host defense is further explored. Dendritic cells (DCs) are immune cells found to be important against numerous pathogens and critical for both innate and adaptive immune responses. In terms of protection against *Candida spp*., DCs can phagocytose and kill ingested *Candida* and produce cytokines in response to *Candida*. In this study, the authors explore whether a specific subclass of DCs ($CD103^+$ DCs) are important for protection against systemic or mucosal Candida infection. The rationale for pursuing these studies is that $CD103^+$ DCs have been found to be critical for parasitic and viral infections and furthermore $CD103^+$ DC dependent IL-12 production has also been shown to be important for helminth infections. Prior to this study, the *in vivo* role of CD103+ DCs in innate immunity against Candida infections has been largely unexplored. The authors leverage the fact that the transcription factor Batf3 is critical for the development of $CD103^+$ CD11b- DCs in order study mice ($Batf3^{-/-}$ mice) that lack $CD103^+$ DCs. Both a systemic (the commonly used *Candida albicans* tail vein injection model that emulates candidemia) and a mucosal (the oropharyngeal candidiasis model) *C. albicans* infection models are utilized. Given that Candida strain-specific differences in antifungal immune responses have been reported *in vivo,*[19] the authors test both laboratory and disease model-appropriate clinical strains.

Interestingly, Batf3 appears to be critical for accumulation of $CD103^+$ DCs in the target organs of their respective disease models (kidney for systemic, tongue for mucosal) and for expansion during systemic and mucosal infections. Yet, deficiency of $CD103^+$ DCs does not reduce survival or fungal clearance during either systemic or mucosal infections. Of note, a recent study showed that Batf3 deficient mice did modulate the host response to a secondary Candida infection.[20] Thus, the role of $CD103^+$ DCs in antifungal host defense during secondary or chronic Candida infections may be important and necessitates future study. This also elucidates the importance of using various infectious models to dissect the role of specific immune effectors.

The scientific focus of a large proportion of microbiology and infectious disease research centers almost solely on the microbial pathogen, yet most infections can only accurately be understood in the context of host-pathogen interactions and dynamics. Many "pathogens," including *Candida spp*., typically colonize the skin or mucosal surfaces of healthy hosts without any deleterious sequelae. If the pathogen invades into the adjacent tissues or spreads into the systemic bloodstream, the host's primary (innate) defense systems have failed, usually as a result of iatrogenic causes or in some cases genetic predisposition. In any case, understanding and unraveling the dynamics of host-pathogen interactions will be critical for devising novel therapies in the future. Thus studies like Break et. al.[18] that elegantly dissect the interaction between the microbial and host immune factors that lead to development of infection are essential for a more holistic appreciation and approach to correcting the often very dysfunctional host-pathogen interactions that have arisen as a consequence of great advances in medical therapies and technology.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

## References

[1] Casadevall A. Fungi and the rise of mammals. PLoS Pathog 2012; 8:e1002808; PMID:22916007; http://dx.doi.org/10.1371/journal.ppat.1002808

[2] Casadevall A, Pirofski LA. Microbiology: Ditch the term pathogen. Nature 2014; 516:165-6; PMID:25503219; http://dx.doi.org/10.1038/516165a

[3] Casadevall A, Pirofski LA. Virulence factors and their mechanisms of action: the view from a damage-response framework. J Water Health 2009; 7 Suppl 1:S2-S18; PMID:19717929; http://dx.doi.org/10.2166/wh.2009.036

[4] Koh AY, Kohler JR, Coggshall KT, Van Rooijen N, Pier GB. Mucosal damage and neutropenia are required for Candida albicans dissemination. PLoS Pathog 2008; 4:e35; PMID:18282097; http://dx.doi.org/10.1371/journal.ppat.0040035

[5] van 't Wout JW, Linde I, Leijh PC, van Furth R. Contribution of granulocytes and monocytes to resistance against experimental disseminated Candida albicans infection. Eur J Clin Microbiol Infect Dis: Off Pub Eur Soc Clin Microbiol 1988; 7:736-41; PMID:3145854; http://dx.doi.org/10.1007/BF01975039

[6] Kuhara T, Uchida K, Yamaguchi H. Therapeutic efficacy of human macrophage colony-stimulating factor, used alone and in combination with antifungal agents, in mice with systemic Candida albicans infection. Antimicrob Agents Chemother 2000; 44:19-23; PMID:10602717; http://dx.doi.org/10.1128/AAC.44.1.19-23.2000

[7] Kullberg BJ, Netea MG, Vonk AG, van der Meer JW. Modulation of neutrophil function in host defense against disseminated Candida albicans infection in mice. FEMS Immunol Med Microbiol 1999; 26:299-307; PMID:10575142; http://dx.doi.org/10.1111/j.1574-695X.1999.tb01402.x

[8] Giles FJ. Monocyte-macrophages, granulocyte-macrophage colony-stimulating factor, and prolonged survival among patients with acute myeloid leukemia and stem cell transplants. Clin Infect Dis: Off Pub Infect Dis Soc Am 1998; 26:1282-9; PMID:9636847; http://dx.doi.org/10.1086/516361

[9] Nemunaitis J, Shannon-Dorcy K, Appelbaum FR, Meyers J, Owens A, Day R, Ando D, O'Neill C, Buckner D,

Singer J. Long-term follow-up of patients with invasive fungal disease who received adjunctive therapy with recombinant human macrophage colony-stimulating factor. Blood 1993; 82:1422-7; PMID:8364195

[10] van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LA, Gilissen C, Arts P, Rosentul DC, Carmichael AJ, Smits-van der Graaf CA, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. New Eng J Med 2011; 365:54-61; PMID:21714643; http://dx.doi.org/10.1056/NEJMoa1100102

[11] Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, Elbers CC, Johnson MD, Cambi A, Huysamen C, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. New Eng J Med 2009; 361:1760-7; PMID:19864674; http://dx.doi.org/10.1056/NEJMoa0901053

[12] Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, Pfeifer D, Veelken H, Warnatz K, Tahami F, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. New Eng J Med 2009; 361:1727-35; PMID:19864672; http://dx.doi.org/10.1056/NEJMoa0810719

[13] Wildbaum G, Shahar E, Katz R, Karin N, Etzioni A, Pollack S. Continuous G-CSF therapy for isolated chronic mucocutaneous candidiasis: complete clinical remission with restoration of IL-17 secretion. J Allergy Clin Immunol 2013; 132:761-4; PMID:23791509; http://dx.doi.org/10.1016/j.jaci.2013.04.018

[14] van de Veerdonk FL, Koenen HJ, van der Velden WJ, van der Meer JW, Netea MG. Immunotherapy with G-CSF in patients with chronic mucocutaneous candidiasis. Immunol Lett 2015; 167:54-6; PMID:25999307; http://dx.doi.org/10.1016/j.imlet.2015.05.008

[15] Bahri R, Curt S, Saidane-Mosbahi D, Rouabhia M. Normal human gingival epithelial cells sense C. parapsilosis by toll-like receptors and module its pathogenesis through antimicrobial peptides and proinflammatory cytokines. Mediat Inflamm 2010; 2010:940383; PMID:20454633; http://dx.doi.org/10.1155/2010/940383

[16] Bahri R, Saidane-Mosbahi D, Rouabhia M. Candida famata modulates toll-like receptor, beta-defensin, and proinflammatory cytokine expression by normal human epithelial cells. J Cell Physiol 2010; 222:209-18; PMID:19780045; http://dx.doi.org/10.1002/jcp.21939

[17] Fan D, Coughlin LA, Neubauer MM, Kim J, Kim MS, Zhan X, Simms-Waldrip TR, Xie Y, Hooper LV, Koh AY. Activation of HIF-1alpha and LL-37 by commensal bacteria inhibits Candida albicans colonization. Nat Med 2015; 21:808-14; PMID:26053625; http://dx.doi.org/10.1038/nm.3871

[18] Break TJ HK, Swamydas M, Lee CR, Lim JK, Lionakis MS. Batf3-dependent CD103+ dendritic cell accumulation is dispensable for mucosal and systemic antifungal defense. Virulence 2016; 7(7):826-835; PMID:27191829; http://dx.doi.org/10.1080/21505594.2016.1186324

[19] Marakalala MJ, Vautier S, Potrykus J, Walker LA, Shepardson KM, Hopke A, Mora-Montes HM, Kerrigan A, Netea MG, Murray GI, et al. Differential adaptation of Candida albicans in vivo modulates immune recognition by dectin-1. PLoS Pathog 2013; 9:e1003315; PMID:23637604; http://dx.doi.org/10.1371/journal.ppat.1003315

[20] Trautwein-Weidner K, Gladiator A, Kirchner FR, Becattini S, Rulicke T, Sallusto F, LeibundGut-Landmann S. Antigen-Specific Th17 cells are primed by distinct and complementary dendritic cell subsets in oropharyngeal candidiasis. PLoS Pathog 2015; 11:e1005164; PMID:26431538; http://dx.doi.org/10.1371/journal.ppat.1005164