



## Commentary

Host Genetics Takes a Toll on Immunity to *Cryptococcus*Cristina Cunha<sup>a,b</sup>, Agostinho Carvalho<sup>a,b,\*</sup><sup>a</sup> Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal<sup>b</sup> ICVS/3B's - PT Government Associate Laboratory, Braga, Portugal

In this issue of *EBioMedicine*, Jiang and colleagues report on the association of genetic variants in Toll-like receptors (TLRs) and the risk of non-HIV cryptococcal meningitis (CM) [1]. CM represents a major cause of morbidity and mortality in HIV-infected patients, especially in sub-Saharan Africa. In recent years however, a growing number of cases has been witnessed among CD4-competent individuals, most of which without any obvious predisposing conditions. This suggests that susceptibility to CM may be, to a large extent, driven by other host or environmental risk factors. Despite the remarkable influence of host genetics on antifungal immune responses, very few studies have addressed the contribution of interindividual genetic variation to the risk of CM, particularly in the absence of HIV infection. Genetic variants in Fc receptors for IgG (FcγR) [2,3] and mannose-binding lectin (MBL) [4] stand out as the most relevant examples correlated with increased susceptibility to non-HIV CM, suggesting a pivotal role of the humoral arm of innate immunity in anti-cryptococcal protection. However, much less is known about the contribution of genetic variants in other pattern recognition receptors to cryptococcal disease.

TLRs are pattern recognition receptors whose activation is responsible for mechanisms involved in pathogen clearance, including the secretion of cytokines and chemokines, and complex immunoregulatory processes leading to the activation of adaptive immune responses. These receptors have been vastly implicated in anti-cryptococcal immunity [5], however the question remains as to which TLR-ligand interaction is actually required for the recognition, phagocytosis, and subsequent fungal killing. In this study, Jiang and colleagues provide both genetic and immunological evidence highlighting the pivotal role of TLR-dependent mechanisms of cryptococcal recognition and cytokine production in defining susceptibility to human CM in HIV-uninfected individuals [1].

The findings reported herein support the exciting possibility for risk stratification and personalized medical interventions, particularly among patients belonging to high-risk populations. However, their immediate clinical translation may be precluded by the limited number of cases of infection that were enrolled and the relative lack of replication in the validation stages. More importantly, the associations described may not be entirely generalizable since these may differ

considerably across patients with different genetic backgrounds. TLRs are known to display a significantly different polymorphic pattern in populations of various ethnic and geographic origins [6], and this may explain the remarkably discrepant results obtained from previous association studies in cohorts of European and Asian ancestry. In addition, common genetic variants account for differences in gene expression among ethnic groups [7], and this may reflect important population-specific effects on gene expression, including TLRs.

Although recent advances have contributed to an expanding number of genetic variants associated with the risk of fungal disease, little is known about their functional consequences through effects on defined biological processes. The study by Jiang and colleagues correlated the presence of genetic variants in TLRs with the levels of cytokines detected in the cerebrospinal fluid (CSF) of infected patients [1]. Besides providing functional validation to the association studies, these findings uncover the potential usefulness of CSF cytokines as diagnostic biomarkers for CM, particularly if combined with fungal surrogate markers and integrating the genetic risk profile of the patient [8]. Moreover, important mechanistic insights can also be drawn from these analyses. In particular, high levels of interleukin (IL)-10 were identified as an independent predictor for disease severity and this finding is reminiscent of recent studies performed in the context of invasive pulmonary aspergillosis and that have identified IL-10 overexpression as an important genetic mechanism of immune suppression contributing to fungal disease [9]. In support of this, the persistent IL-10 signaling in dendritic cells has also been deemed detrimental to cryptococcal lung infection [10], illustrating the diversity of immune mechanisms that may be deregulated by the presence of genetic variants in TLRs.

Several questions remain unanswered, the most relevant regarding the inability to definitively conclude about the impaired molecular and cellular processes that contribute to CM and that may reasonably extend beyond cytokine production. In addition, this study warrants further investigation on the likely interrelationships between different genetic variants across several TLRs and their concerted effect toward the development of fungal disease. A comprehensive appreciation of the mechanisms through which genetic variation in TLRs contributes to CM will provide invaluable insights toward the identification of molecules and signaling networks amenable to therapeutic targeting.

In conclusion, the findings presented in this study represent an important step toward uncovering a genetic susceptibility profile to CM. Recruitment of larger cohorts of patients from different ethnic backgrounds, as well as functional studies dissecting the mechanisms of

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association with infection, are ultimately required. This will certainly attract in the near future an increased focus toward the integration of genetic markers into the clinical practice aimed at the stratification of risk and progression of fungal disease in general and CM in particular among patients at-risk.

### Conflict of interest

The authors declare no conflict of interest.

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### References

- [1] Jiang YK, Wu JQ, Zhao HZ, et al. Genetic influence of Toll-like receptors on non-HIV cryptococcal meningitis: an observational cohort study. *EBioMedicine* 2018;37: 401–9.
- [2] Hu XP, Wu JQ, Zhu LP, et al. Association of Fcγ receptor IIB polymorphism with cryptococcal meningitis in HIV-uninfected Chinese patients. *PLoS One* 2012;7(8): e42439.
- [3] Meletiadis J, Walsh TJ, Choi EH, et al. Study of common functional genetic polymorphisms of FCGR2A, 3A and 3B genes and the risk for cryptococcosis in HIV-uninfected patients. *Med Mycol* 2007;45(6):513–8.
- [4] Ou XT, Wu JQ, Zhu LP, et al. Genotypes coding for mannose-binding lectin deficiency correlated with cryptococcal meningitis in HIV-uninfected Chinese patients. *J Infect Dis* 2011;203(11):1686–91.
- [5] Campuzano A, Wormley FL. Innate Immunity against *Cryptococcus*, from Recognition to Elimination. *J Fungi (Basel)* 2018;4(1).
- [6] Ioana M, Ferwerda B, Plantinga TS, et al. Different patterns of Toll-like receptor 2 polymorphisms in populations of various ethnic and geographic origins. *Infect Immun* 2012;80(5):1917–22.
- [7] Spielman RS, Bastone LA, Burdick JT, et al. Common genetic variants account for differences in gene expression among ethnic groups. *Nat Genet* 2007;39(2):226–31.
- [8] Gonçalves SM, Lagrou K, Rodrigues CS, et al. Evaluation of Bronchoalveolar Lavage Fluid Cytokines as Biomarkers for Invasive Pulmonary Aspergillosis in At-Risk Patients. *Front Microbiol* 2017;8:2362.
- [9] Cunha C, Gonçalves SM, Duarte-Oliveira C, et al. IL-10 overexpression predisposes to invasive aspergillosis by suppressing antifungal immunity. *J Allergy Clin Immunol* 2017;140(3):867–70 [e9].
- [10] Teitz-Tennenbaum S, Viglianti SP, Roussey JA, Levitz SM, et al. Autocrine IL-10 Signaling Promotes Dendritic Cell Type-2 Activation and Persistence of Murine Cryptococcal Lung Infection. *J Immunol* 2018;201(7):2004–15.