Toward the Identification of a Genetic Risk Signature for Pulmonary Aspergillosis in Chronic Obstructive Pulmonary Disease

To the Editor—In this issue of *Clinical Infectious Diseases*, He et al. report on the association of genetic variants in the long pentraxin-3 (PTX3) and risk of pulmonary aspergillosis in chronic obstructive pulmonary disease (COPD) [1]. The management of COPD remains a formidable challenge as the result of the deteriorating lung function sustained by a nonresolving inflammatory response. The steroid therapy required to control inflammation is one major factor triggering the onset of infectious complications. There is thus a pressing demand for innovative prognostic, diagnostic, and therapeutic interventions relevant to disease progression and its complications.

Genetic variation in PTX3 has already been recognized as a major determinant of susceptibility to aspergillosis in stem-cell [2, 3] and solid organ transplant recipients [4, 5]. By validating these findings in COPD patients, He et al. further highlight the potential applicability of PTX3-based genetic markers in predicting infection across patients with intrinsically different predisposing conditions and disease courses. Importantly, the evaluation of the prognostic value of PTX3 variants to risk of infection in other interstitial lung diseases such as sarcoidosis, in which aspergillosis is also a serious complication [6], is warranted.

The clinical translation of these findings to the setting of interstitial lung diseases is however precluded by the limited sample size of the study and the lack of independent validation. In addition, despite positive, the association test results differ considerably from earlier reports. He et al. describe the association of the AA genotype at rs1840680 with aspergillosis in COPD [1], whereas we and others instead demonstrated a role for the GG genotype in stem-cell transplant recipients [2, 4, 7]. We reasoned that this could be due to the different genotype distributions across the individuals of European and Asian ancestry used in these studies or to population stratification issues that the authors did not consider. Even so, it remains unclear why both genotypes impaired the levels of PTX3. Remarkably, common genetic variants are known to account for differences in gene expression among ethnic groups [8]. In this regard, a transcription enhancer encompassing the second exon of PTX3 (including rs1840680) has recently emerged as a fine regulator of PTX3 expression during inflammation [9], whose activity could well depend on the genetic background. The course of infection is also typically different in transplant recipients and COPD patients, and this context specificity may likely impact regulation of gene expression and function. Whatever the mechanism(s) in place, several studies have now confirmed PTX3 as an indisputable genetic marker for risk of aspergillosis across different underlying conditions and ethnicities.

The study by He et al. represents a first step toward uncovering the genetic susceptibility profile of COPD patients to aspergillosis. Recruitment of larger and carefully controlled cohorts of patients, as well as functional studies dissecting the PTX3-driven mechanisms of association with infection, are ultimately required. This will undoubtedly support the integration of these genetic markers into clinically valid processes aimed at the stratification of risk and progression of fungal infection in COPD patients.

Notes

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References

1. He Q, Li H, Rui Y, et al. Pentraxin 3 gene polymorphisms and pulmonary aspergillosis in COPD patients. Clin Infect Dis **2018**; 66:261–7.
2. Cunha C, Aversa F, Lacerda JF, et al. Genetic PTX3 deficiency and aspergillosis in stem-cell transplantation. N Engl J Med **2014**; 370:421–32.
3. Fisher CE, Hohl TM, Fan W, et al. Validation of single nucleotide polymorphisms in invasive aspergillosis following hematopoietic cell transplantation. Blood **2017**; 129:2693–701.
4. Cunha C, Monteiro AA, Oliveira-Coelho A, et al. PTX3-based genetic testing for risk of aspergillosis

after lung transplant. Clin Infect Dis **2015**; 61:1893–4.
5. Wójtowicz A, Lecompte TD, Bibert S, et al.; Swiss Transplant Cohort Study. PTX3 polymorphisms and invasive mold infections after solid organ transplant. Clin Infect Dis **2015**; 61:619–22.
6. Uzunhan Y, Nunes H, Jeny F, et al. Chronic pulmonary aspergillosis complicating sarcoidosis. Eur Respir J **2017**; 49.
7. Fisher CE, Hohl TM, Fan W, et al. Validation of single nucleotide polymorphisms in invasive aspergillosis following hematopoietic cell transplantation. Blood **2017**; 129:2693–701.
8. Spielman RS, Bastone LA, Burdick JT, Morley M, Ewens WJ, Cheung VG. Common genetic variants account for differences in gene expression among ethnic groups. Nat Genet **2007**; 39:226–31.
9. Rubino M, Kunderfranco P, Basso G, et al. Epigenetic regulation of the extrinsic oncosuppressor PTX3 gene in inflammation and cancer. Oncoimmunology **2017**; 6:e1333215.

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