A New Step toward Individualized Antifungal Prevention in Hematopoietic Stem Cell Transplantation

Pierre-Yves Bochud[1,2] and Thierry Calandra[1]

[1]Department of Internal Medicine, Infectious Diseases Service, and [2]Institute of Microbiology, University of Lausanne and Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

(See the article by Plantinga et al on pages 724–32)

Major improvements in our understanding of the innate immune system have resulted from the discovery of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), Nod-like receptors, RIG-I–like receptors, and members of the C-type lectins family expressed by innate immune cells (ie, monocytes, macrophages, or dendritic cells) [1]. Strategically located at the interface of host-pathogen interactions, PRRs play a fundamental role in the sensing of specific microbial molecular patterns and danger signals and in the initiation of innate and adaptive immune responses.

The concept of immunogenetics arose from initial observations, made in the 1940s, that susceptibility to infection was inheritable [2–4] and from the description, in the 1950s, of the first inheritable primary immunodeficiencies [5]. More recently, the availability of high throughput genotyping techniques has opened new perspectives of further improvements of our understanding of the pathogenesis of infectious diseases and of new diagnostic, preventive, and predictive treatment strategies [6–8].

Polymorphisms of PRRs and downstream signaling pathways have been associated with susceptibility to and outcome of infection, suggesting that their detection may have an impact on the prevention or treatment of infectious diseases [6, 8]. Most striking has been the discovery of rare inherited immune deficiencies caused by single, rare polymorphisms in molecules involved in the TLR signaling pathways (*MyD88*, *IRAK4*, *IKK*γ, and *I*κ*B*α) [9–11]. The functional deficiencies associated with these immunodeficiencies are usually dramatic and result in clear cut phenotypes (monogenic inheritance). Typically, affected offspring develop severe and recurrent infection, caused predominantly by pyogenic bacteria. These primary immunodeficiencies clearly illustrate the importance of the TLR-associated signal transduction pathways in host innate immune defenses against infection [6–8].

In contrast, susceptibility to infection in the general population results from polymorphisms of several genes, each having smaller functional contributions (polygenic inheritance). Many studies have reported associations between polymorphisms of innate immune genes (many among TLRs) and susceptibility to infection. However, some of the studies have also yielded inconclusive or conflicting results or findings with questionable clinical implications [6–8]. Several factors may account for a lack of reproducibility. Two of the most critical factors have been the use of imprecise phenotypes of interest and a lack of power because of small sample sizes, especially in the case of polymorphisms with a modest contribution to the phenotype under investigation. Other limitations included the failure to account for important confounders (eg, ethnicity or the use of inappropriate control subjects who do not have a similar risk of exposure), inappropriate statistical methods and analyses (eg, absence of correction for multiple testing), and the absence of validation cohorts or of functional studies assessing the in vitro or in vivo biological impact of the reported polymorphism [6]. Despite all of these potential caveats, some polymorphisms are now emerging that have been associated with specific infections or human diseases. These associations have been replicated, the functional consequences of the polymorphisms have been clearly established, and the polymorphism has been shown to have important implications in the management of patients.

The interesting report by Plantinga et

Received 22 May 2009; accepted 24 May 2009; electronically published 17 July 2009.

Reprints or correspondence: Dr. Pierre-Yves Bochud, Infectious Diseases Service, Dept. of Medicine, Centre Hospitalier Universitaire Vaudois, BH 10-555, rue du Bugnon 46, CH-1011 Lausanne, Switzerland (Pierre-Yves.Bochud@chuv.ch).

Clinical Infectious Diseases 2009; 49:733–5
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1058-4838/2009/4905-0009$15.00
DOI: 10.1086/604715

al [12] in this issue of *Clinical Infectious Diseases* has focused on the impact of an early stop codon polymorphism of the *DECTIN-1* gene in hematopoietic stem cell transplant (HSCT) recipients, which is a patient population among whom infections cause significant morbidity and mortality. Dectin-1 is a transmembrane PRR that specifically recognizes β-1,3-glucans through its extracellular C-type lectin domain and activates several intracellular signaling pathways via an intracellular domain comprising immunoreceptor tyrosine-based activation motifs [13]. Dectin-1 has been implicated in the recognition of several fungal pathogens, including *Candida* [14], *Aspergillus* [15], and *Pneumocystis* species [16]. Upon ligand binding and in concert with TLR2, dectin-1 initiates a cascade of intracellular signaling events that result in cellular immune responses, including phagocytosis, endocytosis, and the production of chemokines and cytokines [14, 17]. In a preliminary study, the authors described an A to T substitution resulting in a stop codon at amino acid position 238 of *DECTIN-1* (Y238X). This polymorphism has a minor allele frequency of 6.9% in the Dutch population. It was first identified in a family in which several members had recurrent mucocutaneous fungal infections.

In the present article, Plantinga et al [12] observed an absence of dectin-1 expression at the monocyte cell surface in individuals who were homozygous for the Y238X polymorphism and a much-reduced interleukin (IL)–1β production by peripheral blood mononuclear cells in response to stimulation with either heat-killed *Candida* species or a combination of β-glucan and Pam3Cys (a TLR2 activator), compared with that for wild-type cells. Data on IL-18 production were less clear-cut than those on IL-1 production and were also somewhat surprising, given that heterozygous cells, compared with homozygous cells, were associated with a more pronounced reduction in IL-18 production. Of interest, the presence of the Y238X *DECTIN-1* polymorphism, found in 13 of 124 assessable Dutch patients who underwent HSCT from human leukocyte antigen–identical siblings, was associated with an increased risk of colonization with *Candida* species (84.6% vs 31.5%). A relatively small sample size, after exclusion of those patients who received antifungal fluconazole prophylaxis, did not allow the study to examine with sufficient power whether the polymorphism was also associated with an increased risk of early candidemia (ie, occurring on or before day 21), which occurred in 18.2% of the patients with and 8.0% of the patients without the Y238X polymorphism ($P = .26$). Likewise, the study was underpowered to detect any impact of the *DECTIN-1* polymorphism on the incidence of mold infection.

Although one might have wished to be provided with additional information about *Candida* colonization (ie, site and amount of *Candida* isolated) and about potential confounding factors, including ethnicity, previous antibiotic exposure, polymorphisms of other PRRs shown to be implicated in the sensing of *Candida* species (for example, TLR2 and TLR4), and validation of the findings in another cohort of HSCT recipients, this clinical observation is strengthened by functional assessment of the impact of the Y238X polymorphism on the responses of innate immune cells to *Candida* species or β-glucan.

The search for risk factors that predispose to infection remains a major challenge in treating immunocompetent hosts. Yet, encouraging progress has been made recently in the identification of genetic factors that are implicated in the development of opportunistic infections in immunocompromised patients, including those undergoing HSCT or solid-organ transplantation. Several recent studies have shown the importance of genetic polymorphisms of *TLR4* [18, 19], *IL-10* [20, 21], or of the plasminogen gene [22] in increasing the susceptibility of immunosuppressed patients to fungal infection. Somewhat paradoxically, immunosuppression did not mask but facilitated the identification of polymorphic alleles that may not have been found to be relevant otherwise. Patients undergoing treatment with novel immunosuppressive drugs, such as anti–tumor necrosis factor agents, constitute another rapidly growing population at risk for severe fungal infections [23]. The study by Plantinga et al [12], linking Y238X polymorphism of *DECTIN-1* with *Candida* colonization, provides a new genetic target for future epidemiological studies, biological investigations, and risk stratification and is a new step forward toward improved predictive and preventive medicine for immunocompromised hosts.

Acknowledgments

Financial support. Swiss National Science Foundation (3100-118266.07), the Bristol-Myers Squibb Foundation, the Leenaards Foundation, and the Santos-Suarez Foundation for Medical Research (to T.C.). P.Y.B. is supported by the Leenaards Foundation.

Potential conflicts of interest. P.Y.B. and T.C.: no conflicts.

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