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Spotlight – corrected manuscript (version 2)

Tracing the origin of invasive fungal infections

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Abstract

Invasive fungal infections are a major cause of mortality in immunocompromised patients. By using high-resolution sequencing, Zhai et al. (*Nat. Med.*, 2020) provide insight into translocation of *Candida* strains from the gut mycobiota to the bloodstream of transplanted patients. Microbiota-driven diagnostic methods could rapidly emerge for preventing deadly fungal infections.

Keywords: High-resolution sequencing, mycobiota, invasive candidiasis, bloodstream infections, dysbiosis

Core text

Globally, the incidence of fungal infections on human health represents a worldwide burden evidenced by worrisome prevalence values of roughly 1 billion superficial mycosis, 20 million allergic fungal diseases, and more than 1 million cases of invasive fungal infections (mainly aspergillosis, candidiasis, and cryptococcosis) [1]. These latter infections are associated with dramatic mortalities, ranging to 20-50%, in spite of currently available powerful antifungal agents [2,3]. Thus, these deadly infectious complications are a strong limitation to medical progress because they occur in the weakest, most susceptible patients. For this reason, it remains important to pursue sustained research to better understand the pathophysiology of deep-seated fungal infections and to develop new strategies for early diagnoses and better targeting of antifungal therapeutic interventions.

Among the various types of fungal invasive complications, bloodstream infections (BSI) by *Candida* yeasts (termed candidemia) are particularly feared in immunocompromised patients such as those who are under chemotherapy or that receive organ transplantation. *Candida* yeasts are widely distributed in nature and various *Candida* species are common constituents of the normal human microflora. However, it is well established that alterations in the host environment, mainly immunosuppression, can promote a transition from a commensal to a pathogenic phase of these opportunistic yeasts [4]. Whereas three decades of active research have provided insight into the pathogenicity mechanisms of prominent *Candida* species, the source of candidemia has been hitherto the subject of considerable debate [5].

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In an exciting new advance, Zhai *et al.* have investigated the dynamic relationship between the human intestinal microbiota and invasive candidiasis. They conducted a nested case-control study in 15 subjects (8 with candidemia and 7 without candidemia) that underwent allogeneic hematopoietic cell transplantation (allo-HCT) [6] and had received antifungal prophylaxis based on echinocandins (micafungin) starting 7 days before transplantation,. An interesting but somewhat alarming first observation was that the *Candida* isolates identified in the blood samples of 6 out of 8 patients belonged to the *Candida parapsilosis* complex (including *C. parapsilosis*, *C. metapsilosis,* and *C. orthopsilosis*). *Candida* isolates recovered in the two remaining patients of this cohort turned out to be *C. albicans* and *C. lusitaniae*, respectively. The *C. parapsilosis* complex shows a lower *in vitro* susceptibility toward echinocandins as compared to *C. albicans*, due to a naturally occurring proline-to-alanine amino acid change in the fungal target Fks1p [7]. This is significant clinical problem, as it seems that the prophylactic regimen has influenced the *in vivo* emergence of less-susceptible *Candida* isolates with serious pathogenic attributes [8].

In spite of previous inquiry, the relationship of intestinal fungi (termed "intestinal mycobiota") with fungal BSI has remained hitherto obscure. Here, Zhai et al. first noticed that among all patients undergoing allo-HCT, only patients that have subsequently developed a candidemia had exhibited a rapid increase of global fungal burden (18S rDNA by a factor of 10^2 - 10^3) in their fecal samples after transplantation. Moreover, high-resolution sequencing analysis suggested that the fungal burden observed in patients that underwent *Candida* BSI was due to the expansion of a single *Candida* species within the mycobiota. Indeed, the fecal *Candida* relative abundance of 7 out of the 8 candidemic patients peaked at 100%, typically before the BSI with the same species (six with *C. parapsilosis* complex species and one with *C. albicans* subsequent candidemia). With the exception of one patient that had an increase of the non-pathogenic *Saccharomyces cerevisiae* yeast species, the control subjects had globally unchanged mycobiota during all the transplantation process with an intestinal fungal diversity comparable to that of healthy people. Thus, these findings show for the first time the relationships between the level of expansion of *Candida* burden in the intestinal tract and the translocation into the bloodstream. Surprisingly, the authors did not detect any *C. lusitaniae* strains in the fecal samples either before or after the onset of the *C. lusitaniae* candidemia in the last patient, suggesting that non-intestinal sources could also promote candidemia in such transplanted patients.

Interestingly, further whole genome sequencing analysis revealed for the first time the relationship between strains expanded in the fecal samples and those recovered in the blood samples of the patients. Therefore, it is highly likely that an intestinal reservoir shaped during the early stages of allo-HCT undergoes random translocation to the blood vessels, leading to candidemia. This relationship was further demonstrated by the clear similarity between genotypes of the fungal strains colonizing the intestine and those found in blood samples.

Finally, this study provides unprecedented evidence of a relationship between *Candida* intestinal expansion and bacterial microbiota by revealing a high relative abundance of *Candida* spp. in the mycobiota associated with lower levels of the total bacterial burden and diversity. More precisely, some bacterial taxa, notably anaerobes that have been previously shown to participate in the resistance toward *Candida* colonization in mouse intestine or those considered to be markers of a "healthy" microbiota, displayed an inverse correlation with a

high *Candida* relative abundance in the samples [9,10]. This particular dysbiosis pattern, probably influenced in part by the antibiotic treatment that the patients received, did not seem so pronounced in patients who did not subsequently developed an invasive candidiasis, even in the control subject in which a *S. cerevisiae* was detected. Taken together, these last results show that specific bacterial communities, likely emerging from an antibiotic-induced gut dysbiosis, may promote the burden of pathogenic *Candida* in the intestinal tract of allo-HCT patients.

As a whole, this enlightening article provides an unprecedented knowledge of the dynamic evolution and association of mycobiota and gut bacterial constituents that precede the occurrence of candidemia in allo-HCT patients (Figure 1). It is important to underline the great potential of the new high-resolution sequencing approaches to unravel such biological scenarios. Beyond their contribution in tracing the origin of invasive fungal infections, we must also anticipate that these new high throughput/deep sequencing strategies may be used in a near future as part of an early diagnosis of the mycobiota destabilization. Certainly, this will have to be considered for better screening of patients at risk of developing candidemia and for starting a targeted antifungal therapeutic intervention in immunocompromised patients.

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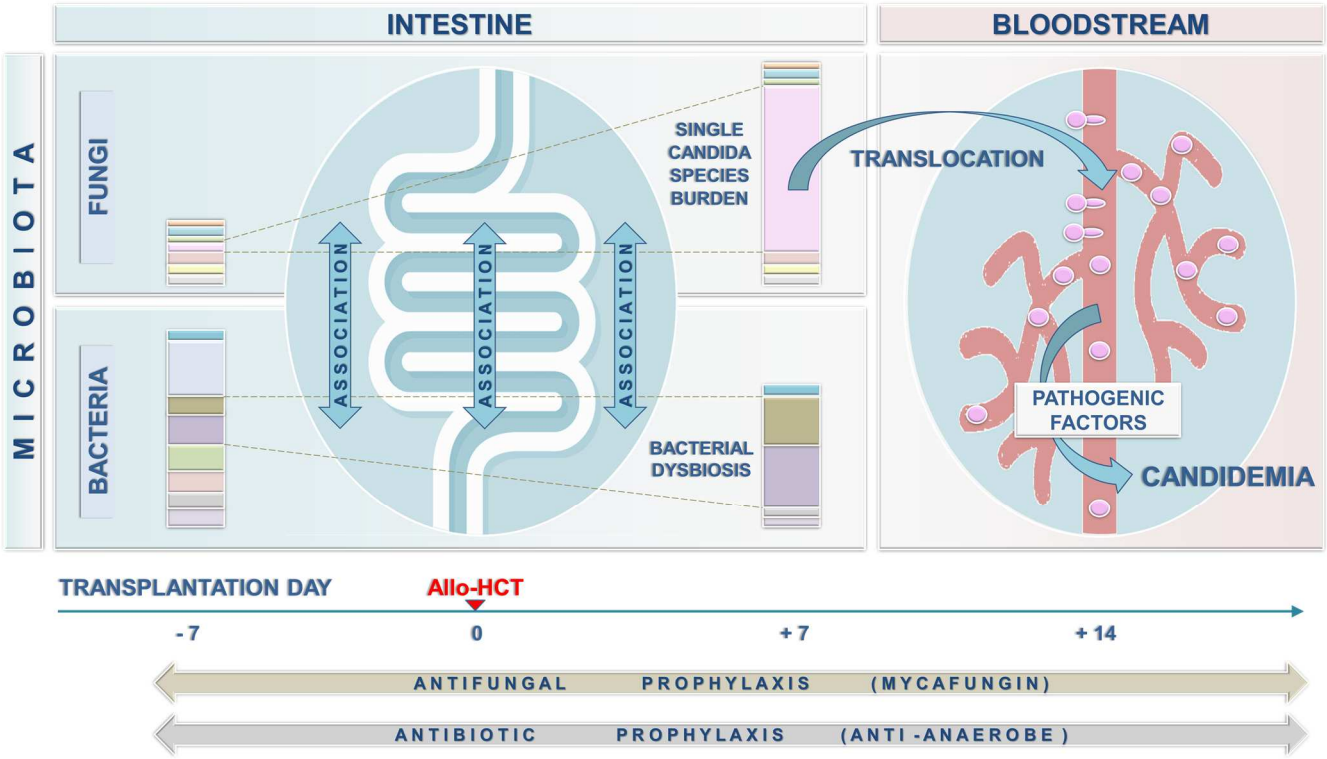


Figure 1. Tracing the origin of invasive candidiasis in allo-HCT patients. Immunosuppression but also antifungal and antibiotic prophylaxis may first promote a dysbiosis in the intestine of the patients. Change in bacterial communities could be associated to the intestinal expansion of pathogenic *Candida* species. Following this fungal expansion, translocation of *Candida* strains from the mycobiota to the bloodstream can occur in transplanted patients.