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Gut mycobiome as a promising preventive and therapeutic target for metabolic disorders

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The human microbiome includes the sum of each and every gene from bacteria, archaea, viruses and eukaryotic microorganisms, such as fungi, that reside the human body, particularly the gut. Gut microbiota play an important role in metabolic homeostasis of the human host [1]. Alterations in the gut microbiota attributed to genetic or environmental factors, such as nutritional factors or medications, e.g. antibiotics or non-steroid anti-inflammatory drugs, may lead to the modulation of the structure or diversity of the gut microbiota, known as dysbiosis [1–6]. Gut microbial dysbiosis has been implicated in the pathogenesis of metabolic disorders, such as obesity, metabolic syndrome, diabetes mellitus type 2, non-alcoholic fatty liver disease, cardio-metabolic disorders and malnutrition [7–12].

Fungi are microeukaryotes accounting for a small part of the human microbiome in comparison to bacteria, forming the so called "human mycobiome". The human mycobiome represents approximately less than 0.1% of the microbial community in the gut [13]. Gut mycobiome and bacteriome are interconnected and may influence each other in a plethora of ways affecting host metabolism.

Gut mycobiome is a tiny but vital and functional part of the gut ecosystem. Alterations of its composition have been associated with a number of diseases such as colorectal cancer, inflammatory bowel disease and irritable bowel syndrome [13]. However, little is known about the composition and long-term stability of the gut mycobiome in middle age and later life as well the interplay between gut fungal and bacterial communities in metabolic homeostasis. Moreover, the relationship between the gut mycobiome and metabolic health is less clear. Indeed, gut mycobiome has been associated with cardiometabolic disorders in animal models and in some human studies [14–17].

In a multiomics and longitudinal study, Dr. Zheng and colleagues investigated how age, diet, and other sociodemographic or clinical factors affect the gut mycobiome by mapping the gut mycobiome among 1244 Chinese middle-aged and elderly adults from the population-based Guangzhou Nutrition and Health Study cohort [18]. They found that considerable gut fungal composition is temporally stable being mainly regulated by age, long-term habitual diet and host physiological state. In particular, they showed that nonsignificant changes over time in 11 genera of the *Ascomycota* (eg, *Pichia, Alternaria* and *Wickerhamiella*) have been observed in 184 study subjects. Many fungal taxa displayed long-term stability even after 3.2 years, suggestive of a core mycobiome which could play a role in the long-term stability of the intestinal ecosystem. In comparison to middle-aged subjects, *Blastobotrys* and *Agaricomycetes* spp were decreased, whilst *Malassezia* was enriched in the elderly group. This study also found that habitual diet may be a significant factor of the mycobiome diversity. Specifically, dairy consumption was a major dietary factor contributing to the variety of the fungal community in the gut, while fruit and fish consumption was not significantly associated with gut mycobiome diversity. This work mirrors Dr. Zheng's previous study on gut microbiome, which has shown that long-term habitual dairy consumption is associated with a higher bacterial diversity, which is an indicator of a healthy gut [19]. Dairy consumption was positively related with *Saccharomyces,* which presents anti-inflammatory properties [20], but inversely linked to *Candida* [18].

Zheng et al. also explored the ecological and functional relationships among gut bacteria, fungi and fecal metabolome, examining whether the interaction between gut bacteria and fungi could modulate metabolic risk. They found that the gut mycobiome may be closely linked to metabolic health through the regulation of gut bacterial functions and metabolites. Interestingly, *Saccharomycetales* spp. interact with intestinal bacterial diversity, being positively related with short-chain fatty acids producers, to influence insulin sensitivity. Furthermore, the presence of *Pichia* fungi contributed to a decrease in serum LDL-cholesterol and total cholesterol levels through the increase of bacterial functional levels and fecal histidine.

These results highlight that the intestinal fungal community is an important component of the gut ecosystem playing a pivotal role in the long-term stability of the gut ecosystem. This integrative cross-kingdom

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analysis may broaden our horizon for novel preventive and therapeutic targets in metabolic disorders. However, more larger multiomics and longer longitudinal studies in other ethnic groups are required to examine the contribution of the gut mycobiome and its interaction with bacteriome and host to the pathogenesis of metabolic disorders.

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Declaration of competing interest

No conflict of interest to disclose.

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Maria Dalamaga*
Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 75 Mikras Asias, Goudi, 11527, Athens, Greece

Liaoyuan Zheng, Junli Liu**
Shanghai Jiao Tong University School of Medicine, Shanghai Jiao Tong University Affiliated 6th People's Hospital, Shanghai Diabetes Institute, Shanghai, China

* Corresponding author.

** Corresponding author.
E-mail address: madalamaga@med.uoa.gr (M. Dalamaga).
E-mail address: liujunli@sjtu.edu.cn (J. Liu).