Review Article

Regulobiosis: A regulatory and food system-sensitive role for fungal symbionts in human evolution and ecobiology

Ju-Sheng Zheng PhD[1,2,3], Mark L Wahlqvist MD[3,4,5]

[1]School of Life Sciences, Westlake University, Hangzhou, China
[2]Institute of Basic Medical Sciences, Westlake Institute for Advanced Study, Westlake University, Hangzhou, China
[3]Institute of Nutrition and Health, Qingdao University, Qingdao, China
[4]Institute for Population Health Sciences, National Health Research institutes, Zhunan, Taiwan, ROC
[5]Monash Asia Institute, Monash University, Melbourne, Australia

The role of microbiomes in human biology and health are being extensively investigated, yet how the fungal community or mycobiome contributes to an integral microbiome is unclear and probably underestimated. We review the roles of fungi from the perspectives of their functionality in human biology, their cross-kingdom talk with other human microbial organisms, their dependence on diet and their involvement in human health and diseases. We hypothesize that members of the fungal community may interact as necessary symbionts with members of other human microbiome communities, and play a key role in human biology, yet to be fully understood. We propose further that "regulobiosis", whereby fungi play a regulatory role in human ecobiology, is operative in humans as probably obtains in other forms of life. Fungally-dependent regulobiosis would characterise, at first, microbiomes which include, but are not limited to, bacteria, archaea, and viruses; then, their human host; and, next, provide ecological connectedness.

Key Words: fungi, mycobiome, regulobiosis, symbionts, human ecobiology

INTRODUCTION

As a highly diverse group of eukaryotes, fungi are ubiquitous and found in virtually all terrestrial ecosystems (Table 1).[1] Recent evidence suggests that fungi may have had a critical role in the colonization of land by eukaryotes, including plants and metazoans (multicellular animals with tissues and organs).[2] Ecologically, fungi may facilitate plant colonisation on land by providing ecological niches, improving substrate availability, augmenting nutrient uptake and increasing above ground productivity.[1] Fungi also appear to be important symbionts or parasites of both vertebrates and invertebrates and involved in the initiation of the evolution of microbiomics and parasitism of animals.[1] It is probable that no plants or animals have been fungus-free during their history of evolution from ancient to modern ecosystems, representing a co-evolutionary history of fungi with plants and animals, including humans (Figure 1).

The knowledge of fungus-human relationship falls well short of that for bacteria, with limited relevant research to inform it. But with recent advances in high-throughput sequencing and bioinformatic annotation tools, the role of fungi in human microbiomics and biology is being steadily revealed.[3] Yet, much about host-fungus interactions remains to be discovered. Those that have been identified in the human gut mycobiome and whether they are known to be symbionts or have functional or health relevance are shown in Table 2.

Firstly, fungi are inescapable, in our food system (as mushrooms or as yeasts and mycelia in fermented foods and beverages),[4] in the human body (in microbiomes) and in our natural and built environments. Fungi are key ecosystem nutrient recyclers, and they facilitate the growth of plants and animals by providing essential nutrients such

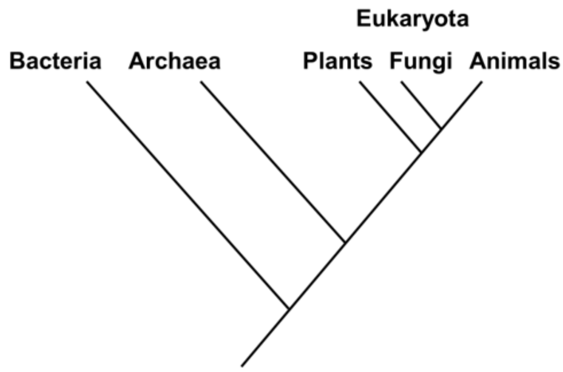

Figure 1. Phylogenetic tree of life: fungi and animals.

Corresponding Author: Dr Ju-Sheng Zheng, School of Life Sciences, Westlake University, 18 Shilongshan Rd, Cloud Town, Hangzhou 310024, China
Tel: +86 (0)57186915303.
Email: zhengjusheng@westlake.edu.cn
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Table 1. Descriptors and definitions

Dysbiosis	Dysbiosis refers to the microbial imbalance or perturbation of normal microbiome on or inside the body
Ecobiology	Ecobiology describes the relationship between living organism and their natural environments
Econutrition	Econutrition is an integrative approach for a better understanding of the interaction between food systems, the environment and nutritionally related human health
Ecosystem	An ecosystem is a combination of living organisms with their nonliving environment, interacting as a system in a given area
Microbiome/microbiomics	A community of microorganism, including bacteria, archaea, fungi and viruses
Mycobiome/mycobiomics	A fungal community within an organism
Regulobiosis	A regulatory role of fungi in regulating the ecosystem of which each terrestrial person is a part
Symbionts	An organism that is closely associated with another organism in a giving environment

as nitrogen and phosphorus from soils and even rocks, largely because of their extensive capacity and diversity of enzyme and bioactive metabolite production.[5,6] Humanity could not survive without fungi.[7-9] One of the most interesting connections with humans is via the fungal sterol, ergosterol, which is converted to vitamin D-2 by ultraviolet irradiation for ingestion as mushrooms, the only non-animal source of the essential vitamin D.[10] Human mycobiomic interdependence is such that, while helminthiasis accounts for much of the global burden of diseases[11] (including protein-energy malnutrition and micronutrient deficiencies), not only are some fungi ovicidal for helminths,[12,13] but helminthiasis can be associated with mycobiomic modulation or even depletion.[14,15]

Secondly, they have played an important role in modern medicine, notably the discovery of the world's first antibiotic, penicillin, from the mould Penicillium[16,17] and the availability of fungally-derived statins for the management of hypercholesterolaemia and cardiovascular diseases.[18] Fungi are promising sources for the discovery of new antibiotics or of innovative strategies for infection control; fungally produced defensins, like plectasin, are an example.[19,20] Their products and metabolites are myriad and are likely to provide further opportunities for preventive and therapeutic medicine.

Although the fungal community is a "minority" microbiota within the human body, accounting for less than 0.1% of gut microbiota,[21] fungi hold considerable promise for their regulatory roles in human biology. Just like the queen bee in a beehive or the captain of a ship, we perceive a central role for fungi in biological regulation or "regulobiosis" (Figure 2). This reflects what have been downstream and lateral evolutionary consequences for them with an interdependence with all forms of life. Although principally terrestrial rather than marine, their multiple types, their extensive functional plurality, and their system resilience are of wide biological consequence.[22] These features signify a regulatory role of fungi in modulating the ecosystem of which each terrestrial human body is a part. We refer to this as "human ecobiology", recognising that we are ecological creatures.[23] Fungi have an econutritional significance which embraces us.[24]

In this review, we briefly summarise the known relationships between fungi, human biology and health, and describe our hypothesis for the fungus-human relationship.

Functionality of fungi in humans: energy homeostasis and immunomodulation

Microbiomic function relevant to human health would appear to include the regulation of energy homeostasis and metabolism.[25] Gut microbiota-derived short-chain fatty acids (SCFAs), including acetate, propionate, butyrate and lactate, are produced in the host as energy substrates, absorbed into the bloodstream and can be a pathway to metabolic disorders.[25] SCFAs affect host lipogenesis, gluconeogenesis, stimulate gut peptide (glucagon-like peptide-1 and peptide YY) secretion, and regulate immunity, adipogenesis, inflammation and proneness to cancer.[25,26] Although SCFAs are mainly derived from gut bacteria, their production may be subject to a regulatory role of fungi. Fungi may indirectly modulate SCFA status via their crosstalk with the SCFA-producing bacteria. Alternatively, gut fungi may more directly modulate the host's bacterial metabolite profile. Indications that this may be so come from gut metagenomics which recognise fungi-bacterial mutualism in association with SCFA status,[14] but the relevant fungal metabolite research lags that of the bacteria. Also possible is that fungus-produced volatile aromatics play a role in modulating their micro-environment and interacting with the host.[27,28] Moreover, fungal circadian clocks within the gut may be interactive with the human host and affect energy regulation, given that biological clocks have been found to be conserved from fungi to animals including humans.[29]

The close interaction of gut mycobiota with host immunity has been systematically reviewed elsewhere.[30] As an adaptive immune response to gut fungi, induction of antibodies reactive to *S.cerevisiae mannan* (ASCAs, Anti-Saccharomyces cerevisiae mannan antibodies) are considered a classical readout of the immune effect of intestinal fungi, and the ASCA titers are higher in patients with gastrointestinal diseases.[31-33] Gut fungi may be also involved in the induction of immune tolerance, and oral, vaginal and systematic infection with *C.albicans* is linked to the Treg cell induction, protecting the host from disease.[34,35] Both adaptive immune responses and innate immune memory could be primed by *C.albicans* in the gut, suggesting that strain-specific features could inform the host immune response.[36,37] Fungi-induced Th17 cells may not only play an important role in antifungal immunity during mucosal fungal infections, but also have roles in homeostasis and inflammation.[37] Overall, gut mycobiota exert their protection against systemic bacterial and fungal infection via trained immunity and adaptive immune responses. However, the study of mycobiota-

Table 2. Major fungi identified in human gut

Gut fungi	Potential role
Candida	Human symbionts (*Candida albicans*, *Candida sake*); some *Candida* species were increased in patients with inflammatory bowel diseases[74], irritable bowel syndrome[61], alcoholic hepatitis[64,65] or neurological diseases (autism spectrum disorders, schizophrenia, rett syndrome)[66]
Cryptococcus	Human symbionts
Malassezia	Human symbionts (*Malassezia restricta*, *Malassezia sympodialis*, *Malassezia globosa*); *Malassezia sympodialis* was lower in patients with inflammatory bowel disease[74]; *Malassezia* was higher in colorectal cancer patients[75,76]
Trichosporon	Human symbionts; *Trichosporon* was higher in colorectal cancer patients[75]
Saccharomyces	Human symbionts (*Saccharomyces cerevisiae*, *Saccharomyces pastorianus*); food-associated fungi; *Saccharomyces* was decreased in patients with alcoholic hepatitis[65]; *Saccharomyces cerevisiae* is used clinically as a probiotic, with a protective effect against inflammatory discorders, decreasing bacterial growth and colonisation; *Saccharomyces cerevisiae* was lower in patients with inflammatory bowel diseases[74] and colorectal cancer[76]
Cyberlindnera	Human symbionts (*Cyberlindnera jadinii*)
Penicillium	Human symbionts; food-associated fungi (*Penicillium roqueforti*); *Penicillium* was decreased in patients with alcoholic hepatitis[65]
Cladosporium	Human symbionts
Aspergillus	Human symbionts; some *Aspergillus* species are producers of carcinogens and enriched in colorectal cancer patients[76]
Agaricus	Human symbionts (*Agaricus bisporus*)
Fusarium	Human symbionts
Pichia	Human symbionts
Debaryomyces	Human symbionts (*Debaryomyces hansenii*); Food-associated fungi (*Debaryomyces hansenii*); *Debaryomyces* was decreased in patients with alcoholic hepatitis[64]
Galactomyces	Human symbionts (*Galactomyces candidum*)
Alternaria	Human symbionts (*Alternaria alternata*)
Clavispora	Human symbionts
Malassezia	Human symbionts (*Malassezia globosa*)
Kluyveromyces	Human symbionts; food-associated fungi
Moniliophthtora	Human symbionts; *Moniliophthtora* was higher in colorectal cancer patients[76]
Rhodotorula	Human symbionts; a potential pathogen; *Rhodotorula* was higher in colorectal cancer patients[76]
Acremonium	Human symbionts; an opportunistic pathogen; *Acremonium* was higher in colorectal cancer patients[76]
Thielaviopsis	Human symbionts; *Thielaviopsis* was higher in colorectal cancer patients[76]
Pisolithus	Human symbionts; *Pisolithus* was higher in colorectal cancer patients[76]

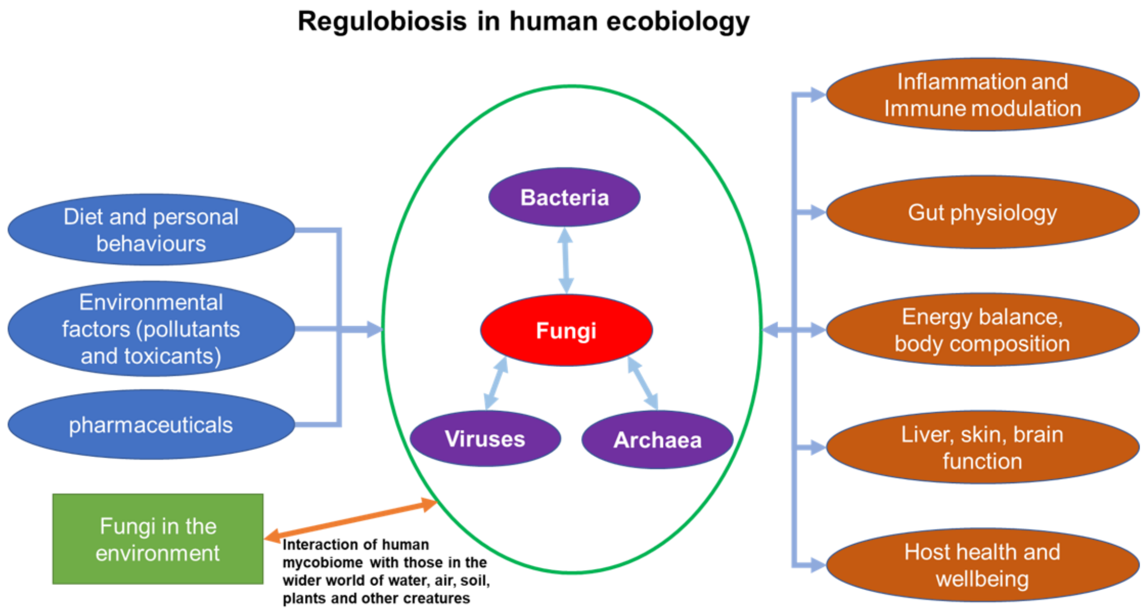

Figure 2. Conceptual framework for fungal "regulobiosis" in human ecobiology.

immunity relationships is still in its infancy, with mechanistic study limited to very few fungal strains of non-intestinal origin. Furthermore, the role of cross-kingdom interaction of fungi with other microbial communities on host immunity is unclear.

Inter- and intra- relationships of the fungal mycobiome with other human microbial communities

The cross-kingdom interaction of fungi with other microbes in the human microbiome is largely unknown. There is some in-vitro evidence suggesting the wide existence of fungi-bacteria interplay.[38-40] The potential mechanisms involved in fungi-bacteria interaction are physical interaction, chemical interaction and release of metabolic byproducts, influence on the environment, competition, and biofilm formation.[38] The above mechanisms embrace various cross-kingdom relationships, such as mutualism, commensalism, amensalism, parasitism and competition in a variety of human organs, mainly the mouth, lung, gut and vagina.[3] Some bacteria appear to inhibit fungal colonisation and growth through their metabolites,[41,42] while other bacteria could promote fungal persistence in the intestine.[43] Evidence from a limited set of fungal strains indicates that gut mycobiota may exert colonisation resistance to prevent the colonisation of the intestine by exogenous bacteria.[44-46]

By contrast, the relationship of fungi with other microbial communities such as archaea, viruses, or helminths in humans is less clear and the evidence sparse. Particularly, the interaction of helminth parasites with fungi merits future investigation, given the available evidence for a major impact of intestinal helminth parasites on the bacterial microbiota.[47]

A recent study clearly supports our regulobiosis hypothesis.[48] Using a novel computational framework for cross-kingdom joint analysis and targeted amplicon sequencing data for human lung and skin micro- and mycobiomes, it has been found that fungi play a stabilizing role in human ecological network organization.[48] This fits well with our regulobiotic concept and indicates a fundamental role for fungi in human ecobiology. More evidence will be needed to demonstrate whether this microbiomic stabilizing role of fungi exists in other body sites, such as the gut and reproductive tract in men and women.

Interaction of fungi with diet and human health

Unlike that for bacteria, the influence of diet on human fungal system structure and composition and their correspondence with health outcomes is less well investigated, although the evidence is emerging. For example, animals fed high-fat diets exhibit changes in overall fungal and bacterial microbiome structures,[49] which suggests a role of fungi in the gut microbiome-obesity association. While bacteria are involved in nutrient absorption, like that of vitamin B-12, and are interactive with diet, the evidence for fungi is missing. It has been suggested that gastrointestinal fungi simply represent oral and dietary sources, with little or no gastrointestinal colonisation.[50] However, extensive mycobiomic profiles of the human gut are available which are unlikely to be only reflective of current food intake.[50,51] That dietary macronutrients and plant food orientation can affect gut mycobiome composition predicates relationships between dietary patterns, food cultures and microbiomically-driven health and well-being.[51-53] In infants, Candida may be detected in the microbiome,[54] which may be maternally acquired and responsible, for example, for nappy rash. It is likely that mycobiomic status is associated with necrotising enterocolitis in neonates.[55,56]

Clinical experience has generally regarded the fungi and health nexus as one of invasive fungal infection[57] or the adverse effects of mycotoxins,[58] with the role of mycobiome in human health maintenance and in chronic disease development poorly understood.[59] Thus, with traditional culture-dependent methods, Candida species are found to be associated with inflammatory bowel diseases, namely Crohn's disease, ulcerative colitis and other forms of gut inflammation.[60] Using culture-independent methods, other fungi found in the gut mycobiome have been identified as pathogenetically relevant to, not only gastrointestinal diseases such as irritable bowel disease,[61-63] but also alcoholic hepatitis[64,65] and inflammatory disease in general.[30]

Emerging evidence highlights the potential role of gut mycobiome in the gut-brain axis.[66] Fungal dysbiosis has been observed in central nervous diseases (e.g., autism spectrum disorders and schizophrenia). A proposed mechanism is that gut fungi may produce SCFAs, which could decrease the blood-brain barrier permeability, attenuate the influence of cytokines (produced at gut sites, then crossing the blood-brain barrier) on susceptible brain areas.[67-69] Other potential mechanisms might include direct modulation of the immune system or interaction with the wider microbiome, especially gut bacteria also linked to brain function.[66]

Fungi and food security

At each point in the food system, fungi can play a role in its productivity, efficiency and sustainability.[7] Fungi contribute to soil health and that of the livestock and food plants dependent on it. They themselves serve as foods. They can contribute fuels for energy required in food handling. They can assist in preservation through fermentation and add utility in food processing. Nutrient recycling from food waste requires them. Prospects for their provision of biodegradable packaging alternatives to plastic and cardboard are emerging,[7] so reducing overall food-related waste. In the meantime, fungal products can degrade the plastic now contaminating the food and water systems.[70] Fungi can and do play a fundamental ecological role in food security.[71] Particularly apposite to food and health security is the temperature optimum for fungi and how different it is from the warm-blooded mammalians with which they associate.[72] We know for plants and most of the animal kingdom that this aspect of homeostasis is critical. Global warming may radically disrupt the human mycobiomic relationship.

Perspective and hypothesis for fungus - human relationships: regulobiosis

The relationship between fungi and human biology and health, and the role of fungi has been underestimated. Relevant research, ranging from the animal mechanistic to the human translational has lagged its bacterial counterpart. Much the same could be said of archaea which also form part of the microbiomic complex.[73] "Regulobiosis" as a conceptual framework provides a platform for enquiry about the place of fungi in ecobiology and its health implications when disordered. Candidate disruptors, which fungi may attenuate or accentuate, include climate change (such as temperature), dietary and other personal behaviours, pollutants, concomitant illness and organ failure, and therapeutic agents. If fungal networks and diversity provide wide and pervasive biological surveillance and resilience, more attention may need to be paid to their optimisation. This will apply ecologically close to us and remote from us, as do our mycologically interdependent livelihood requirements with fungal ubiquity.

Fungi have played a critical role in the initial land colonisation by eukaryotes and the long history of co-existence of fungi with plants and animals, including modern humans. Our regulobiosis hypothesis is fostered by the co-evolutionary history of fungi and human beings. According to this hypothesis, fungi are likely to be an essential component of the human microbiome and ecology and play a crucial role in human health maintenance. No longer would fungi be seen as peculiarly health-threatening, but ecologically integral to us. Their collective and participatory ecobiological capacity might enable us to devise more innovative health approaches to the major burden of disease, mostly related to nutrition and infection. This comes at a time of the growing threats of food insecurity and antibiotic resistance with increased population density, ecosystem loss and climate change, each liable to challenge our regulobiotic capability.

AUTHOR DISCLOSURES

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