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Analysis of Biological İnteractions between Bacteria and Fungi in the Human Body

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ABSTRACT

Both bacteria and fungi have the ability to significantly influence global biogeochemical cycles. Both positive and negative interactions can occur between bacteria and fungi. Numerous microorganisms, mostly bacteria but also fungi, viruses, and archaea, make up the human body's microbiota. A large network of both positive and negative interactions between fungi and bacteria contributes to both human gain and damage. While an amount of data has been published on bacterial relationships, far less data is known on the interactions of bacteria with another component of the fungal community. Therefore, our goal is to examine and evaluate the biological relationships that exist between fungi and bacteria in the human body. According to the findings of our review, all polymicrobial interactions may be categorized as synergism, predisposition, microbial interference, and addition, regardless of whether they are solely bacterial, fungal, or cross-kingdom.

1. Introduction

Together, fungi and bacteria make up about 15% of the biosphere's biomass (Bar-On Y.M., 2018), making them powerful agents of global biogeochemical processes, such as the breakdown of organic materials. It is anticipated that these creatures' common saprotrophic habits would encourage competition. Therefore, it should come as no surprise that fungal–bacterial competition was shown to be one of the main factors influencing microbial communities all over the world, including those found in the human gut (Coyte K.Z., 2015) terrestrial soils, and maritime environments (Bahram M., 2018). Nonetheless, research on fungal-bacterial interactions over the last two decades has revealed a number of non-competitive interactions (Olsson S., 2017; Pawlowska T.E., 2018) , which may also help to stabilize and structure fungal and bacterial communities and act as global biodiversity determinants (Tu C., 2019; Nakazawa T., 2020). We refer to these non-competitive relationships as symbioses. Mutualisms, commensalisms, and exploitative interactions are examples of the "living together of dissimilar organisms" that might vary in the balance of fitness costs and benefits experienced by the interacting species (Pawlowska T. E., 2024).

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Fungal–bacterial symbioses are a component of a much larger network of both beneficial and detrimental interactions between the soil-associated microbiota and its plant and animal hosts, which in turn support the health of ecosystems all over the world (Berg G., 2020). As a result of a growing understanding of these complexities, research on the interactions between fungi and bacteria is becoming more comprehensive. For instance, bacteria and fungi provide 12 and 7 gigatons of carbon, respectively, to the soil (Bar-On Y.M., 2018), creating a huge space for interactions. Interestingly, the same soil bacteria can form several alliances at the same time or in succession.

Numerous microorganisms, mostly bacteria but also fungi, viruses, and archaea, make up the human body's microbiota. Together, these populations create intricate and dynamic ecosystems. The microbiota is regarded as an unquestionable player in human health because of its many roles. As the principal microorganisms found in the human microbiota, bacteria have been extensively researched and linked to the development of pathologies as well as the preservation of homeostasis (Nibali L., 2016). Despite being less prevalent than bacteria, fungal communities are still crucial to both health and illness (Limon J.J., 2017).

Numerous microorganisms, including bacteria, viruses, fungus, and archaea, make up the complex ecosystem that is the human gut (Hoffmann C., 2013; Hamad I., 2016). The bacterial component of the human gut microbiota is typically the focus of studies, but there is growing recognition of the significance of the other components, particularly the fungus component, or so-called mycobiota. The prior lack of focus on mycobiota has been caused, among other things, by the low density of fungus in the gut relative to bacteria. The number of cultivable fungi is between 102 and 106 CFU/g, whereas the number of bacteria is between 1011 and 1012 CFU/g. Approximately 0.1% of the entire microbial metagenome is made up of fungal genes (Maas E., 2023).

For a variety of reasons, but mostly because there is a smaller scientific community interested in these subjects and fewer databases containing the whole genomes of fungus, the fungal population of the microbiota is still not well understood. Technical issues also exist, such as DNA underrepresentation in samples and contamination with the host's eukaryotic DNA (Kruger W., 2019). Microorganisms in the microbiota naturally interact with one another as members of an ecosystem. Although interspecies bacterial interactions have received a lot of attention lately, fungi and bacteria share habitats and can communicate with one another. Furthermore, a number of investigations have connected certain bacterial-fungal interactions to the onset or severity of illness (Lapiere A., 2022). So, our aim is to review and analyze the biological interactions between bacteria and fungi in the human body.

2. Bacterial-fungal interactions

All over nature, microbial communities inhabit a variety of environments and display a wide range of interactions between and among species, ranging from competition and predation to symbiosis (Coyte K.Z., 2015). The human body is one ecological niche of special importance since it is home to a variety of bacteria, fungi, viruses, and archaea that interact to control various facets of human health (Kapitan M., 2019; Santus W., 2021). In particular, these microbial communities are essential for preserving regular physiological processes because dysbiosis of the microbiota is linked to a number of illnesses, such as cancer (Caruso R., 2020), irritable bowel syndrome (Jeffery I.B., 2020), diabetes (Tig H., 2014), obesity (Turnbaugh P.J., 2009), and cancer (Helmink B.A., 2019), as well as allergies (Liu H.Y., 2020). These commensal organisms can be acquired through birth, diet, and exposure to a variety of settings; as a result, they can significantly affect a person's health and development throughout the course of their lifetime. Crucially, a variety of phenotypic features are influenced by interactions between microbiota members and the host. However, our knowledge of how these players communicate is still in its infancy, despite the significance of these conversations (Ferretti P, 2018).

Polymicrobial Interactions

Regardless of whether they are purely bacterial, fungal, or cross-kingdom, all polymicrobial interactions fall into one of the following

categories. The first is synergism, in which a microorganism establishes a habitat for another to colonize or infect. Second, one germ interacts with the host during predisposition, making it more vulnerable to colonization by the second microbe. Third, the initial microbe's host interaction minimizes or stops a second germ from colonizing or infecting the host during microbial interference. Antagonism is another term for this decrease or avoidance. Lastly, addition occurs when two ordinarily non-pathogenic bacteria only cause illness when combined (Brogden K.A., 2005; Rall G., 2016).

These four categories suggest that interactions between fungi and bacteria affect more than only the host. The interaction of bacteria and fungus can also be influenced by the host or the surrounding environment. Different niches have different oxygen levels, nutrient supplies, and interactions with the host immune system. This in turn affects the local microbial community's makeup and behavior. Many bacteria and fungi change their metabolic state and virulence potential as they transition from high-diversity homeostasis to low-diversity dysbiosis. As a result, many cross-kingdom combinations of microbial interactions are conceivable, and the level of antagonism or synergism varies with each combination. The fundamental mechanisms of fungal-bacterial interaction include chemical or physical contact, host or environment modification, competition for nutrients or adhesion sites, and the development of mixed species biofilms. These mechanisms may alter depending on the host's niche. Combined biofilm production is more likely to have a detrimental effect on the host during colonization or infection, whereas competition for the host adhesion site is more likely to have an antagonistic effect. It is currently impossible to accurately forecast how a particular bacterial and fungal combination would work in a particular host niche, even with the growing number of research. Additionally, the way interactions occur in vitro does not necessarily accurately reflect how they will play out in the human host (Krüger W., 2019).

Mutualisms and symbioses

For more than a century, researchers have examined how commensal and pathologic bacteria affect human health, finding several direct links to both symbiotic and disease states (Libertucci J., 2019). Although our knowledge of bacteria has advanced significantly, we still don't fully grasp fungal commensalism. Fungi, now separately referred to as the mycobiome, were not considered an essential component of the human microbiome until recently. Furthermore, we are only just beginning to recognize the positive functions these microorganisms play in our lives because of the growing use of antimicrobials and the harm they inflict to our microbiome. Exploring the interaction between bacterial and fungal populations in relation to human health has become more important as technology advances and our awareness of the effects of microorganisms on human physiology and disease grows (Kirtishri M., 2021).

The best way to think about mutualism is as reciprocal exploitations that nonetheless benefit each party in the end. Many mutualistic systems are important as ecological and evolutionary novelties because of their emerging characteristics. For instance, a significant evolutionary shift underpinning organismal complexity was the eukaryotic cell's endosymbiotic beginning (López-García P., 2023). One partner increases fitness in commensalisms whereas the other has no net impact (Mathis K.A., 2020). Many of these beneficial interactions can serve as facilitations at the community level (Pawlowska T. E., 2024) where the existence of one species modifies the environment in a way that improves the growth, survival, or reproduction of another species that is spatially and temporarily connected (Bronstein J.L., 2009).

One party gains an advantage at the expense of the other in exploitative symbioses, such as parasitism. Predation, also known as fungivory/mycophagy (de Boer W., 2005), can also be seen as a component of the symbiotic continuum due to comparable fitness results. Crucially, in fungal-bacterial interactions, it can be challenging to distinguish between the processes underpinning competitiveness and exploitative relationships, which have negative effects on both parties (Pawlowska T. E., 2024). Specifically, our observations of patients with chronic wounds have indicated that fungi and bacteria co-inhabit

the wound bed to enhance antibiotic resistance and pathogenicity (Kirtishri M., 2021).

In a 2016 research, Kalan et al. (2016) used an in vitro model to show that bacterial and fungal cells interact closely, with bacteria forming the perimeter of the biofilm and yeast cells forming the core. According to this hypothesis, the bacteria acquire antibacterial resistance from the protective fungal matrix, while the fungi gain virulence factors (such as the capacity to produce extracellular enzymes and generate hyphae) (Kalan L., 2016). Escherichia coli/Staphylococcus aureus and Candida albicans have been shown to interact similarly (De Brucker K., 2015; Kong E. F., 2016).

Streptococcus mutans and Streptococcus viridans were the two most prevalent bacterial species found, providing yet another illustration of mutualisms and symbioses. Specifically, S. mutans is a kind of bacterium that is frequently identified in tooth biofilms (Metwalli K. H., 2013). The production of extracellular polysaccharides (EPS) by the exoenzyme glucosyltransferase is thought to be the source of this organism's pathogenic potential (Falsetta M. L., 2014). By sticking to surfaces and eventually producing an acidic environment, this enzyme creates biofilms that eventually result in the development of dental plaques (Metwalli K. H., 2013). According to in vitro research, the presence of Candida albicans causes glucosyltransferase B to be expressed more often. This enzyme then attaches itself to the surface of the Candida albicans and causes an extracellular matrix to develop (Falsetta M. L., 2014). Additionally, antifungal medications like fluconazole are sequestered by EPS, making C. albicans resistant to the medicine (Kim D., 2018). Finally, large concentrations of S. mutans were caused to proliferate by fungal compounds such farnesol (Kim D. S. A.-B., 2017).

It is known that a number of additional species work in concert with Candida albicans to cause infections and oral candidiasis (Diaz P. I., 2012). According to XuH. (2016), Streptococcus oralis, Streptococcus sanguinis, and Streptococcus gordonii have been linked to intensifying C. albicans infections and causing the pathogenic yeast to spread deeply throughout the body. Furthermore, it has been discovered that Candida albicans can intensify the development of anaerobic bacteria in aerobic environments, which might worsen gingivitis. Additionally, if a person with oral lichen planus also has a concurrent C. albicans infection, their symptoms may worsen since they have a chronic inflammatory disease. Although steroids are commonly used to treat lichen planus, they may encourage more confluence of Candida albicans, making detection and therapy difficult for these individuals (Karkowska-Kuleta J., 2018).

3. Competition

The depletion of a shared resource or reciprocal interference through the production of toxic metabolites are two examples of negative competition consequences (Granato E.T., 2019). It referred to all as antagonisms because of the issues with the mechanical differentiation between competitive and exploitative interactions. Crucially, the results of the interactions that populations of the interacting species encounter might change over time and within the symbionts' spectrum of distribution. Whether fungal and bacterial partners coexist in host-associated or free-living microbial communities, this trend is anticipated to be true (Pawlowska T. E., 2024).

In contrast to the above-mentioned synergistic relationships, microorganisms can also interact antagonistically, with one organism potentially preventing the growth of another (Rall G. a. K., 2016). The environment and the host may have further effects on the suppression or expansion of microbial development, which would add even another level of complexity. The antagonistic or synergistic effects of different microorganisms are dynamically influenced by these parameters. The host may experience dysbiosis as a result of the prevalence of particular species and variances in biodiversity, rendering the host susceptible to a range of pathologic diseases (Kapitan M., 2019).

While certain bacterial species release substances that prevent fungal virulence features such as filamentation and biofilm formation, many bacterial species prevent the development of Candida albicans (Forster T.M., 2016; Nogueira F., 2019).

The interaction between C. albicans and Escherichia coli in mice was evaluated in one of the first investigations evaluating the pathogenic effects of a combined bacterial–fungal infection. Interestingly, if a sublethal dosage of E. coli was given intravenously or intraperitoneally prior to a lethal dose of C. albicans, attenuation in host death by C. albicans was noted. This was consistent with in vitro results that demonstrated E. coli's capacity to gradually lower C. albicans vitality (Peleg A., 2010). The mechanism behind these results was not explained, though. On the other hand, greater lethality was shown (mostly) if the E. coli was administered after the C. albicans inoculation, which was believed to be mediated by E. coliendotoxin. Similar findings have since been reported by a number of other researchers, who found that endotoxin appeared to play a significant role in the heightened pathogenicity induced by concurrent infection with C. albicans and E. coli as opposed to death by either organism alone. Since E. Coli and Candida albicans are commensals of the human gastrointestinal system and are frequently identified in intra-abdominal and hospital-acquired bloodstream infections, these findings have clinical significance. These findings also suggest that in cases of invasive candidiasis, appropriate antibiotic treatment may be crucial (Peleg A., 2010).

P. aeruginosa is commonly found in the lungs of people with cystic fibrosis (Berube B.J., 2016), and is a major source of hospital-acquired infections, such as pneumonia and urinary and wound infections (Leclair L.W., 2010). In actuality, P. aeruginosa persistently colonizes more than 75% of CF patients over the age of 18, and this colonization frequently lasts the patient's whole life. According to earlier research, Candida albicans affect P. aeruginosa pathogenicity, biofilm formation, and antifungal chemical release. In particular, C. albicans generates farnesol, a quorum-sensing molecule that suppresses transcription from the pqsA–E operon, prevents the quinolone signal PQS from being produced, and eventually suppresses the expression of genes involved in the biosynthesis of phenazine (Cugini C., 2007). However, the presence of the fungus increases the production of phenazines through an unidentified pathway in P. aeruginosa–C. albicans biofilms, where P. aeruginosa and PQS concentrations are high. This suggests that the effects of C. albicans on P. aeruginosa are complex (Cugini C. M. D., 2010). It's interesting to note that by preventing iron uptake, Candida albicans can likewise affect P. aeruginosa virulence. Proteins released by Candida albicans suppress the expression of P. aeruginosa genes, such as pyochelin and pyoverdine, which are crucial for iron uptake and virulence (Lopez-Medina E., 2015). Mice were adequately protected against P. aeruginosa infection by oral administration of C. albicans secreted proteins, and oral iron supplementation restored bacterial virulence when C. albicans was present. In the lungs of individuals with cystic fibrosis, P. aeruginosa, and A. fumigatus frequently co-colonizers (Leclair L.W., 2010) and the gliotoxin that A. fumigatus produces prevents P. aeruginosa from growing and forming biofilms (Reece E., 2018). According to other research, A. fumigatus secretes isocyanides that have broad-spectrum antibacterial action, including potential against P. aeruginosa, and bind copper (Raffa N., 2021).

Last but not least, structural features of partner body plans and their life cycles—which vary significantly between bacteria and fungi—have an impact on the development and maintenance of symbiotic relationships, including mutualisms and antagonisms. Bacterial life cycles, in example, contain solitary planktonic cells that develop into biofilms, which are collections of highly integrated, matrix-bound, socially interacting cells (Nadell C.D., 2016). The metabolic differences between planktonic and biofilm-bound organisms might give biofilms emergent characteristics like enhanced resistance to antibiotics. Biofilms are thought to house up to 80% of prokaryotic cells on Earth (Flemming H.-C., 2019). On the other hand, yeasts and/or hyphae are examples of terrestrial fungal growth types. Although bacteria and fungus have different body plans, certain yeasts and fungi that are linked with animals may create biofilms, just like bacteria (Kernien J.F., 2018). Furthermore, in the setting of human illness, mixed fungal–bacterial biofilms are not unusual (Peters B.M., 2012). On the surface of fungal hyphae, bacteria can also create biofilms (Peleg A.Y., 2010).

4. Discussion

Global ecosystem functioning depends heavily on the diversity of microbial communities (Wagg C., 2019; Le Provost G., 2021). Additionally, it is becoming clear that microbial diversity influences how these systems react to the disruptions caused by global change (Bardgett R.D., 2014). We still don't fully grasp the mechanisms behind the dynamics and structuring of microbial communities, though. The traditional community ecology of macroorganisms may provide some insights, but it's crucial to keep in mind that many microbial life cycles are significantly shorter than those of plants and animals, which influences the rate of change and adaptation (Pierce E.C., 2021; Cosetta C.M., 2023). The ecology of macroorganismal communities is based on a variety of models that support neutral theory and niche theory. The mechanisms cited by neutral theory and niche theory (Pocheville A., 2015) are increasingly seen as extremes of the same continuum of biological diversity-promoting activities. The ecological niche is a multidimensional hypervolume where each point corresponds to a state of the biotic and abiotic environment that allows the species to exist indefinitely. Niche theory attributes stable coexistence of competing species to their separation along various axes (dimensions) of the niche (Pocheville A., 2015; Pawlowska T. E., 2024), Neutral theory, on the other hand, holds that all species are equal and susceptible to random events like immigration, speciation, and extinction. While extinction reduces variety, immigration and speciation are thought to stabilize it (Chisholm R.A., 2020).

In many niche theory models, antagonistic interactions play a crucial role. While niche partitioning and natural enemies preserve species diversity, competitive exclusion is predicted to reduce it (Chisholm R.A., 2020). Similar to this, models created especially for microbial communities place a strong emphasis on antagonistic relationships, arguing that although antibiotic interactions preserve diversity, competition stabilizes the gut microbiome (Coyte K.Z., 2015; Pawlowska T. E., 2024).

The cutaneous and mucosal surfaces, including the skin, the mouth cavity, the gastrointestinal system, and the lower female reproductive tract, are where bacteria and fungus are most frequently found when there is no illness. Disease at these locations can result from localized insults, such as burn injuries to the skin, poor dental hygiene, surgery, or oral or gastrointestinal mucositis following chemotherapy. These illnesses are frequently polymicrobial in origin (Baena-Monroy T., 2005; Gupta N., 2005). These germs may also spread into typically sterile areas, such as the bloodstream, as a result of breaches in tissue barriers. Similar to vaginal candidiasis, which can develop following the use of systemic antibacterials, systemic insults to human microbial ecology, such as antimicrobial therapy or host immunity deficiencies, can cause an imbalance in the normal microbial flora and enable a normally benign, commensal organism to turn pathogenic. Additionally, patients with chronic lung diseases (McAlester G., 2008) and those on mechanical ventilation in intensive care units (Azoulay, 2006; Rosenthal, 2006), where mixed bacterial–fungal biofilms are frequently observed, are particularly susceptible to bacterial and fungal colonization of the respiratory tract. Polymicrobial biofilms can also have an impact on in-dwelling medical devices that penetrate the skin (Peleg A.Y., 2010).

Fungi were long underestimated and underdiagnosed as pathogens. In particular, fungi that co-isolated with bacteria were frequently regarded as inconsequential since they were thought to be unrelated to environmental pollution or to change the course of the illness (Brown G.D., 2012). Once more, new research describing the co-isolation of bacteria and fungus from patient material was prompted by better diagnosis and greater awareness. According to their findings, bacterial-fungal interactions during infections are common. According to Herman et al., the yeast was found with and without accompanying bacteria in around 8% of the 68,000 clinical samples that tested positive for Candida spp. According to other research, mixed infections accounted for up to 38% of candidemia cases (Kim S.H., 2013; Reno J., 2015). In bronchoalveolar lavage cultures from patients with cystic fibrosis (CF), Pseudomonas aeruginosa is more commonly found in those with persistent Aspergillus fumigatus infection or persistent Candida albicans colonization than in those

without these fungi (Amin R., 2010; Krüger W., 2019).

Advances in sequencing technology have made it easier to identify and characterize other members of these microbial communities in the human gut (Li, 2018; Kapitan M., 2019), and other anatomical sites (Kalia N., 2020). whereas traditional human microbiome studies have concentrated on bacterial species. The opportunistic fungal pathogens are one type of commensal microbe. Over 1 billion individuals are reportedly infected by these eukaryotic infections each year, resulting in roughly 1.5 million fatalities globally (Fisher M.C., 2018). In order to cause a variety of diseases, such as superficial infections of the skin, hair, and nails; chronic fungal lung infections; and systemic infections with mortality rates as high as 90%, the majority of human fungal pathogens exploit local or systemic immune system suppression (Fisher M.C. G. S., 2020). Aspergillus, Cryptococcus, and Candida species are the three primary opportunistic invaders that can cause systemic illness in humans. Some of these species, such as Aspergillus fumigatus and Cryptococcus neoformans, are exposed to humans through environmental reservoirs. Candida albicans, which inhabit the skin, urogenital tract, and gastrointestinal tract, is one of the human microbiota's components that causes other fungal illnesses (d'Enfert C., 2009). It should come as no surprise that bacterial pathogens that can live inside a human host are also the cause of a considerable amount of morbidity and mortality in humans. Examples of these pathogens include Clostridium difficile in the gut, Pseudomonas aeruginosa in the lungs, and Staphylococcus aureus in the nasopharyngeal cavity (Foster T.J., 2014), and Clostridioides difficile in the gut (Dicks L.M.T., 2019). Although the importance of bacterial-fungal interactions in opportunistic infections has been somewhat clarified by recent research (Mould D.L., 2021), little is known about the mechanisms via which these interactions contribute to pathogenesis. Bacterial-fungal interactions in the setting of the human host have also been examined in a number of recent papers (Kapitan M., 2019; Santus W., 2021).

Nevertheless, there is also an ecological theory that suggests that, when combined with antagonisms, positive interactions such as mutualisms (Tu C., 2019; Nakazawa T., 2020), commensalisms (Mougi A., 2016) and community-level facilitative interactions can stabilize diverse communities of macroorganisms. The Stress Gradient Hypothesis specifically highlights the function of facilitative interactions in dry and semi-arid ecosystems, among other hard physical settings. Crucially, global change is predicted to increase the number of such adverse situations globally (Pawlowska T. E., 2024).

It must synthesize pertinent information about fungal–bacterial symbioses studied in reductionist pairwise settings (Mazzocchi F., 2012), place them in a broader ecological context, and highlight important knowledge gaps in order to support the development of experimental strategies required to clarify the role of symbiotic interactions in the organization and dynamics of microbial communities. When taken into account, symbioses can have a variety of fitness outcomes, such as mutualisms or antagonisms. These include collaborations where endosymbiotic/endobiotic bacteria (EB) live within fungal cells as either ephemeral symbionts (Pawlowska T.E., 2018) or well adapted symbionts (Araldi-Brondolo S.J., 2017).

5. Conclusion

Worldwide, fungi and bacteria coexist in a vast variety of host-associated and free-living microbial communities. They are also essential to ecosystems' ability to operate. Coexisting organisms in a specific habitat that interact with one another are referred to as ecosystems; this description fully captures the relationships inherent in the human microbiota. Through symbiotic and antagonistic behaviors—most notably, the use of metabolites as communication elements—these interactions mold communities of microorganisms. In order to comprehend the function of interactions in bacterial-fungal communities, this review highlights factors that must be taken into account. Bacteria and fungi can metabolically interact through many molecules or metabolic pathways in a number of significant symbioses that are poorly understood at the mechanistic level. These interactions can have a variety of impacts on the development of their counterparts. The majority of articles on bacterial-fungal interactions concentrate on how they affect

pathogenic organisms and the emergence of diseases, seldom ever discussing how they contribute to health maintenance. To illustrate the important importance of these interactions in health, more study is required on how bacterial-fungal crosstalk affects and preserves homeostasis.

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