Interactions between potentially pathogenic fungi and natural human microbiota

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ABSTRACT. The human body is composed of $10^{14}$ cells, of which only 10% of them belong to the human host itself: the remaining 90% are microorganisms. Commensal microorganisms are necessary for the proper functioning of the human body and covers an area that could potentially become sites of adhesion of pathogenic microorganisms, it thus represents a form of competition for potential pathogens. The coexistence of fungi and bacteria in cases of systemic infections is a significant diagnostic and therapeutic problem, and the human immune system reacts differently, depending on the pathogen. Numerous publications exist concerning the relationship between microorganisms belonging to different ecological groups, the majority of which concern the interaction between macro-organisms and potential pathogens, or the synergistic relationship between parasitic species. However, there is still too little information concerning the role of natural microbiota in maintaining homeostasis and the relationships between particular species inhabiting the human organism.

Key words: bacteria-fungi interactions, human microbiota, *Lactobacillus*, *Candida*, biofilm

Natural human microbiota

The proper functioning of the human body depends not only on genetic material, and somatic processes, but also on the balance between the body and the microorganisms colonizing it. The human body is composed of $10^{14}$ cells, of which only 10% of them belong to the human host itself: the remaining 90% are microorganisms, including indigenous types – commensals, typical for the host, and allochtonous types derived from the outside the body, which are often pathogenic [1]. Assuming that the human body can be regarded as an ecosystem inhabited by many organisms, attention should be paid to the relationship between the host and its microbiota. A complex commensals–host system is made possible by the ability of cells to communicate. The microbiota responds to physical and chemical signals from macroorganisms concerning, among other things, the nutrient availability, pH and metabolism products of the host. Conversely, the microorganisms can regulate gene expression and the formation of the structure of host tissues, thus influencing many physiological processes of their host [2].

The last decade has seen a growth of interest in the nature of the mutual relationship between the human body and the microorganisms colonizing it, which is referred to as the microbiome. In 2007, work began on the „Human microbiome” project, whose aim is to investigate the human microbiome under physiological and pathological conditions. As up to 80% of the species included in the microbiota fail to respond to culture with standard laboratory methods, most of the project is based on genetic analysis techniques, particularly 16S rRNA sequences. The project involves sequencing the genetic material at least 3000 species of bacteria, and so far, 800 genomes have been analyzed; 18 ontocenoses have been analyzed in women and 15 in men [3–5].

No taxa have been found which occur in all test subjects and which inhabit all ontocenoses, however, the species composition of the oral cavity ontocenosis is similar across the human population with highest number of taxa being found in the
Actinobacteria pregnancy, especially of biodiversity rises significantly in women during caused by diet and the place of origin of the people. Individuals: the few differences being mainly relatively little diversity of biota between 3 years of age, after which time the number of taxa demonstrate a large number of species, but many species of bacteria being present in the intestine. The smallest number of cells and a biodiversity of microbiota, particularly in the development have been observed in the number and isolated from 90% of all vaginal samples [6].

3% of those surveyed. In contrast, in the elderly above was identified in 46%, and 1% of total cell count, Bacteroides thetaiotaomicron was identified in 46%, and Bacteroides fragilis in 16% of those surveyed. In contrast, Escherichia coli represents 0–0.1% of all microorganisms isolated from 61% of subjects, while Lactobacillus crispatus, L. iners, L. gasseri and L. jensenii were isolated from 90% of all vaginal samples [6].

Changes related to the stage of human development have been observed in the number and biodiversity of microbiota, particularly in the intestine. The smallest number of cells and a relatively small variety occurs in newborns, despite many species of bacteria being present in the amniotic fluid. Species diversity grows rapidly up to 3 years of age, after which time the number of taxa increases only slightly. In contrast, adults demonstrate a large number of species, but relatively little diversity of biota between individuals: the few differences being mainly caused by diet and the place of origin of the people. Biodiversity rises significantly in women during pregnancy, especially of Propionibacterium and Actinobacteria, and returns to its pre-pregnancy stage after delivery. In contrast, in the elderly above 65 years of age, the number of Bacteroides significantly increases, and the variety depends on dietary habits [7].

The surface of human mucosa have been found to host yeast and yeast-like fungi, especially of the genus Candida. C. albicans is the most frequently isolated, although in recent years, the prevalence of C. glabrata, C. krusei, C. parapsilosis, C. tropicalis and C. dubliniensis has increased. Although the fungi are isolated from healthy individuals, their appearance and colonization of the human organism are always associated with the violation of homeostasis. In the human body, fungi occur in two morphological forms: yeasts (Y) and filamentous (M). As the filamentous form is considered the more pathogenic, due to its higher enzymatic activity, it is regarded as one of the indicators of virulence of the strain. Switching forms from Y to M allows the fungi to produce biofilm, damage human cells mechanically and to penetrate deep into the tissue [8–13].

**Formation of biofilm**

Microorganisms form a biological membrane referred to as biofilm on the surface of the mucous membranes and skin. Its formation starts with the settling of the bacteria on the surface. Adhesion is related to the physical interactions between the surface and the bacterial fimbriae and cilia. After a single layer of microbial cells covers the substrate, the cells begin to intensively produce a thick extracellular matrix (EPS), which is responsible for the maintenance and operation of the bacterial structure and the control of its metabolic processes. The bacteria lose their cilia and proliferate to form a multilayered microcolony surrounded by the EPS. Free DNA molecules found in the extracellular matrix contribute to the horizontal transfer of genes, which may lead to cell resistance to antibiotics in the biofilm. A system of channels allows for transportation of organic compounds and the removal of metabolites within the surface layers of the biofilm. Cells in the inner layers have limited access to nutrients and oxygen, but are exposed to the toxic effects of waste products, and therefore their activity is greatly reduced or completely inhibited [14].

Fungi also may produce biofilm on various surfaces, but not all species form the mature structure. Saccharomyces cerevisiae only adheres to the substrate, but does not develop a three-dimensional membrane. The ability to produce a biofilm is characteristic for the genus Candida and is associated with the virulence of the strain. A Candida biofilm is frequently formed on the synthetic material used for the manufacture of catheters and prostheses, even within 48 hours from the adhesion of the first cells to a silicone or acrylic substrate. During maturation, budding cells are extended to pseudohyphae, forming a network surrounded by exopolysaccharides. Two signaling molecules are of great importance in the formation
of a biofilm: farnesol, which inhibits the formation of hyphae, and tyrosol, which stimulates the development of pseudohyphae [15]. Colonisation by Candida is also observed on mucosal surfaces, such as the intestine, in the case of bacterial biota eradication. Experiments using gnotobiotic mice showed that during one-time contact, Candida albicans is not able to effectively colonize mice with a normal microbiota, while a high level of colonisation (86–100%) was found after 7 days after fungal inoculation in animals lacking bacteria [16].

When the microbial balance in the human body is normal, a multi-species biofilm is formed in which the individual microorganisms are forced to interact. However, the composition and diversity of the microorganism community forming the biofilm depends on its place of occurrence, as its collective metabolism must be adapted to make the fullest possible use of available nutrients. Adaptation is facilitated by an efficient intercellular communication system based on secreted signalling molecules. The mobilisation of metabolic processes is dependent on the secretion of autoinducer, a signalling molecule, by a sufficiently large number of cells. This is known as quorum sensing and concerns communication of cells belonging to one or many species [17].

The role of natural microbiota

Commensal microorganisms are often necessary for the proper functioning of the human body. Microbes may regulate the expression of host genes, thus affecting the metabolic processes in epithelial cells [1]. Peptidoglycan, a component of the cell wall of bacteria, stimulates the development of lymph follicles in the intestine to form lymph nodes and B lymphocytes producing IgA. The lipopolysaccharides and peptidoglycans of commensal bacteria stimulate the production of mucus by the epithelial cells. Similarly, butyrate secreted by microorganisms can also be used as a nutrient by the epithelial cells. [18]. In addition, the intestinal microbiota plays an important role in the digestion of proteins, starch and cellulose. Fibrin decomposition is carried out by fermentation, leading to the formation of propionic, butyric and acetic acid, as well as hydrogen, carbon dioxide and methane. The resulting fatty acids lower the pH of the intestinal contents, stimulate the growth of the epithelium and absorption of calcium, iron and magnesium, and also are toxic to pathogens. Intestinal bacteria also synthesize group B vitamins and vitamin K [18,19]. The products of bacterial metabolism are involved in the synthesis of cholesterol, lipogenesis and gluconeogenesis. Thus, disturbances in the composition and functioning of biota are associated with the occurrence of obesity, type 2 diabetes and atherosclerosis.

Under conditions of proper homeostasis, butyric acid produced by the microorganisms inhibits the growth of cancer cells by induction of apoptosis or inhibition of cell division [20]. The metabolites and cell components of commensal bacteria penetrate from the mucus layer to the epithelial cells and alter the expression of the genes responsible for the production of antimicrobial agents. The Bacteroides and Lactobacillus genera inhibit the inflammatory response in intact mucosa by suppressing the secretion of NF-κB. A correct microbiota stimulates the production of interleukin IL17, IL22, and IL23, which activate an early immune response in the case of pathogen infection, and regulates T_H-cell maturation [18].

The host organism constitutes a living environment rich in nutritional substrates. Both the skin and mucous membrane, which are exposed to the external environment, are covered with a biological membrane in the form of multi-species biofilm. As the natural biota covers an area that could potentially become sites of adhesion of pathogenic microorganisms, it thus represents a form of competition for potential pathogens. It also stimulates the immune system for continuous production of antibodies, which increases the rate of response in the event of infection [8,19].

The propagation and development of pathogens originating from the external environment is limited by bacteriocins produced by commensal microorganisms. The metabolites of Lactobacillus genus bacilli reduce the pH to levels unfavorable to infiltrating pathogenic microorganisms and regulate the activity of bacterial enzymes. Lactobacillus sp. are also known to produce hydrogen peroxide, which has been demonstrated to have antimicrobial activity [21].

Ghannoum et al. [22] report the presence of fungi possessing unfavorable factors, typically of the genus Candida, in 10–70% of people. Oral mycobioti analysis based on the detection of genetic material showed that 36% of fungi can not be detected by standard methods (culture). Candida species were isolated from 75% of samples, Cladosporium sp. – 65%, Aureobasidium sp. and
Saccharomyces sp. – 50%. Less frequent genera were Aspergillus sp. (35%), Fusarium sp. (30%) and Cryptococcus sp. (20%). The presence of fungi is not evidence of an ongoing disease process, but their penetration into the organism and colonization of mucosa is always associated with the disturbance of homeostasis, including the taxonomic balance of natural microbiota. The presence of competitive bacterial biota inhibits the excessive proliferation of fungi, thus establishing a balance between the components of the oncocenosis. However, any violation of this state may lead to the proliferation of fungal cells, colonization of a larger mucosal surface and eradication of commensal bacteria, leading ultimately to the development of fungal infection.

Interaction natural microbiota–fungi

Pro- and antifungal activity of bacteria

The penetration of fungi into the human organism and their settling in the mucosa is the result of the aggregation and adhesion of fungal and bacterial cells to each other. The Streptococcus sanguis and S. salivarius colonizing the oral cavity are characterized by a weak potential to aggregate with C. albicans and so inhibit the formation of pseudohyphae. A similar relationship was observed in the case of Bacteroides melaninogenicus [23]. In contrast, S. gordonii stimulate the attachment and growth of fungi [24]. Experiments in vitro have demonstrated that the cells of C. albicans, C. tropicalis and C. glabrata adhere more readily to a layer constructed by S. mutans, Fusobacterium nucleatum or Actinomyces viscosus, rather than directly to the substrate. Only 1% of fungal cells possess the ability to co-aggregate with bacteria [23]. In addition, C. albicans was observed to adhere to Actinomyces naeslundii and Fusobacterium nucleatum within the dental plaque, and Peptostreptococcus sp. was found to aggregate within the tooth root, which favors the development of dental caries and periodontal disease [25].

The coexistence of C. albicans with Streptococcus oralis (streptococci typical for oral cavity) increases the invasiveness of fungi into the tissues of mammals and induces apoptosis of cells of the mucosa as a result of damage to the trans-membrane proteins of epithelial cells [26]. Streptococcus gordonii stimulates Candida biofilm formation by the production of muramyl dipeptide, a nutrient for fungi which regulates their virulence. C. albicans adheres to a proline-rich protein receptor on streptococci, while relations with staphylococci are likely regulated by an adhesin sequence similar to agglutinin [21,27,28].

Peters et al. [29] observed a positive correlation between the formation of pseudohyphae and adhesion of Staphylococcus aureus to C. albicans cells. More than ten times of bacteria adhered to the cells of hyphae than budding cells in a mature biofilm. It was found that 56% of S. aureus cells in a sample were associated with elements of the mycelium, compared to 25% of S. epidermidis, and Streptococcus pyogenes, 17% of Pseudomonas aeruginosa, 5.7% of Escherichia coli and 2.5% of Bacillus subtilis cells. The mutualistic relationship between S. aureus and C. albicans explains the frequent coexistence of these species in up to 20% of cases of diseases of the mouth, vagina or hospital candidemia. The relationship between these species is expressed also in mutual stimulation of virulence by regulation of gene CodY expression [29].

Harriot and Noverre [28] demonstrate that S. aureus develops a biofilm only with C. albicans strains capable of assuming a filamentous form; there is not such possibility with strains which occur only in the form of blastospores. The presence of the filamentous stage is required to obtain resistance to vancomycin by S. aureus. It was also shown that strains of C. albicans coexisting with the bacteria are resistant to amphotericin B [28]. Metabolites of S. aureus stimulate the formation of dichotomous branching in Aspergillus fumigatus and vesicular protrusions at the ends of A. terreus hyphae [30].

Over 75% of women have suffered from vaginal candidosis, caused by C. albicans at least once in their lives (90%). In most cases, mycosis occurs as a result of a decrease in the number of lactobacilli. As a large Lactobacillus population prevents the colonization of the vagina by fungi, recent years have seen research into their potential use as therapeutic agents. Gil et al. [31] observed increased Lactobacillus sp. aggregation around cells of C. albicans, C. glabrata, C. krusei and C. tropicalis, which may contribute to an increase in the concentration of antifungal compounds. Furthermore, different Lactobacillus species were found to produce different amounts of lactic acid and hydrogen peroxide, which inhibit the growth of fungi. Similar studies conducted by Strus et al. [32] show that Lactobacillus sp. inhibits the growth of C. albicans, but does not affect the development of
C. pseudotropicalis. The study also identifies Candida strains resistant to hydrogen peroxide. In contrast, the aggregation of lactobacilli with C. albicans reduces the adhesion of bacteria, but increases the adhesion of fungi to the synthetic vaginal ring, which is an alternative to standard oral contraceptives [33].

Besides hydrogen peroxide, Lactobacillus sp. produce organic acids, diacetyl compounds and bacteriocins with antifungal activity. These are mainly compounds with a low molecular weight of less than 1000 kDa, and include (S)-(−)-2-hydroxyisocaprylic acid, hydrocinnamic acid, phenylactic acid, decanoic acid, azelaic acid, 4-hydroxybenzoic acid, p-coumaric acid, vanillic acid, DL-P-hydroxyphenyllactic acid and 3-hydroxydecanoic acid. Reuterin (3-hydroxypropionaldehyde), produced by L. reuteri, also has antifungal properties and inhibits the growth of Aspergillus fumigatus and A. niger. Guo et al. [34] report its effectiveness against the dermatophytes such as Microsporum canis, M. gypseum and Epidermophyton floccosum, which are insensitive to most standard drugs used. Platelet assays indicate that a combination of L. reuteri and L. brevis and also, a combination of L. casei and L. arizonensis inhibit the growth of such dermatophytes, producing a zone of inhibition against E. flocossum of up to 35 mm [34].

Typical of the colon microbiota, the Escherichia coli rod causes infections of the urogenital tract, particularly in women. It was found that E. coli stimulates adhesion of C. albicans to the urinary bladder mucosa, thereby increasing the risk of candidosis. On the other hand, the intestinal microbiota produces large amounts of mucus which contains factors which inhibit C. albicans adhesion to the walls of the gut [25]. Tests based on animal models demonstrate that subjects inoculated intravenously with lethal numbers of C. albicans cells demonstrate lower mortality if first inoculated with Escherichia coli, which may suggest the inhibition of C. albicans virulence by bacteria. Conversely, when the subjects were inoculated with E. coli after the injection of fungal cells, the mortality of animals was found to increase, which is probably associated with the action of the E. coli endotoxin [35].

Both live and dead Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Staphylococcus aureus, Streptococcus pyogenes and S. salivarius cells inhibit biofilm formation by C. albicans. It has been shown that the presence of Gram-negative bacteria influences the morphological structure of the biofilm by reducing the expression of genes responsible for fungal pseudohyphae formation, whereas the Gram-positive bacteria does not change the architecture of the Candida biofilm [36]. Pseudomonas aeruginosa cells colonize Candida pseudohyphae, then secrete phenazines and phospholipase C, which are toxic to the fungi [35].

The growth of A. fumigatus and A. niger is restricted by pigments produced by Pseudomonas aeruginosa: pyocyanine, 1-hydroxyphenazine and a green fluorescent pigment. In addition, 1-hydroxyphenazine also inhibits the production of A. fumigatus, A. flavus, A. niger and A. terreus spores. It was found that the production of pigments by Pseudomonas is closely linked to the presence of fungi which reduce the concentration of iron ions, but increase the content of asparagine to the value required by the bacteria [30]. 3-oxo-C12-acyl homoserine produced by P. aeruginosa inhibits the formation of pseudohyphae by C. albicans.

It has been shown that as many as 238 fungi genes exhibit altered activity in the presence of bacteria. Elevated expression has been noted for 109 genes related to, among other things, the transport of drugs (SNQ2, CDR11) and production of proteins responsible for the dispersion of the biofilm (YWP1), while the remaining 129 genes, primarily related to adhesion and the properties of the biofilm (the ALS gene group and RBT), demonstrate reduced expression [37].

Other metabolites of P. aeruginosa, pyocyanine and phospholipase C, demonstrate a fungicidal action against yeast cells. The minimum inhibitory concentrations (MIC) for pyocyanine and 1-hydroxyphenazine were found to be 100 μg/ml and 25 μg/ml, respectively, against yeast, compared with 100 μg/ml and 50μg/ml against Aspergillus fumigatus [38]. The red pigments of P. aeruginosa, aeruginosins A and B and their precursor, 5-methylphenazine-1-carboxylate (5MPCA), are known to have reducing properties and to penetrate the yeast cell, and have been found to exhibit antifungal activity against the hyphal form of C. albicans: in a mixed culture with Pseudomonas, the survival rate of C. albicans decreases from 86% to 3–10% [39]. Kerr [40] reports that candidosis was inhibited by P. aeruginosa in cystic fibrosis patients, which later recurred after successful administration of fluconazole, to which the isolated strains of C. albicans were susceptible. Laboratory tests have shown that the growth of other Candida species: C. krusei,
C. kefyr, C. guilliermondii, C. tropicalis, C. lusitaniae, C. glabrata and C. parapsilosis, and Saccharomyces cerevisiae, can also be limited by *P. aeruginosa* [40].

Rods of the genus *Salmonella*, responsible for typhoid fever, enter the human organism from the environment. Despite being non-sporulating rods with a limited ability to survive unfavorable conditions outside the host, infection of *Salmonella* serotype *enteridis* was observed by the consumption of almonds which had been contaminated years earlier. Analysis of this phenomenon has led to the discovery of the relationship between the *Salmonella* cells and hyphae of *Aspergillus niger*, which is present in large amounts in soil, water and organic surfaces. Laboratory experiments have confirmed that within one hour of contact, bacterial cells overlap the hyphae with a multilayer biofilm while planktonic cells attempt to attach themselves to the forming structure. No such relationship exists between *A. niger* and other species, such as *Escherichia coli*, *Pseudomonas chlororaphis* and *Pantoaea agglomerans*. Biofilm formation on the hyphae of *A. niger* by *Salmonella enterica* is associated with the production of cellulose and the presence of spiral fimbriae that adhere to the chitin comprising the fungal cell wall and allows bacteria to survive outside the human organism. N-acetylglucosamine also plays a role in the binding of bacteria and hyphae, which is likely to facilitate a similar relationship between *Salmonella* and *Aspergillus* in the tissues of the host [41].

*Klebsiella aerogenes*, a common urinary tract pathogen, is able to stimulate melanisation of *Cryptococcus neoformans* when present on the same substrate, even without direct contact. This ability to produce melanin is a virulence marker of fungi of this genus, with a eumelanin-type pigment being formed from kinin and free radicals in a reaction catalyzed by laccase. In this case, *K. aerogenes* produces dopamine, which is then used as a precursor for *C. neoformans* to produce melanin in the laccase-catalysed reaction. Other species of bacteria, such as *E. coli*, *K. pneumoniae*, *Enterococcus aerogenes* and *E. cloaca* do not affect fungal cell melanisation as they have no tyrosinase, which converts tyrosine to catecholamines [42].

**Pro- and antibacterial activity of fungi**

Fungi can be a component of the natural microbiota, but their presence is always associated with the risk of excessive proliferation when the commensal bacteria populations are eradicated. Mason et al. [16] found that within seven days of the completion of antibiotic therapy, the populations of *Lactobacillus* and *Enterococcus* in mouse intestine are restored. A greater presence of *C. albicans* has been found to both suppress the growth of *Lactobacillus* sp., and increase the proliferation of *Enterococcus faecalis*, which predominates in this ontocenosis, even after 21 days following the end of treatment. Although they are found to be sensitive in *in vitro* tests, increased resistance to drugs of them is also observed *in vivo*. Both *C. albicans* and *E. faecalis* may have a similar relationship in the human organism, and it can promote the spread of antibiotic resistance in bacteria [16]. Hipp et al. [43] showed that while *C. albicans* inhibits the growth of *Neisseria gonorrhoeae*, others including *C. tropicalis*, *C. parapsilosis*, *C. glabrata* and *Trichosporon cutaneum* do not exhibit similar activity.

Stimulation of *Staphylococcus aureus* by *Candida albicans* has also been shown in a mouse model. Within 48 hours of an intraperitoneal administration of a combination of *S. aureus* and a sub-lethal dose of *C. albicans*, the bacterium is detectable in the blood and different organs, and the mouse die. A similar effect has been observed when inactivated fungal cells are used, while the introduction of bacteria alone does not cause the death of the animals. The changes in the tissues caused by a combination of fungi and bacteria are the same as those caused by the fungi alone. When co-invading, a large number of *Staphylococcus* cells is accompanied by a small number of fungi, suggesting that the fungi stimulate the virulence and allow the spread of *S. aureus* in the peritoneal cavity [35].

Ovchinnikova et al. [44] demonstrated that *S. aureus* adheres to the end and middle parts of pseudohyphae in greater numbers and with more adhesive force than the initial section, which is caused by the presence of pseudohyphal cell wall proteins with the agglutinin sequence ALS3. The presence of *C. albicans* promotes the formation of the biofilm by *S. aureus*. The resulting bacterial microcolony formed on the layer of fungal cells, and the matrix surrounding the staphylococci, demonstrate a closer similarity to the fungal parts, suggesting that it is created by *Candida*. While bacteria in a mixed biofilm exhibit increased resistance to vancomycin, the resistance of the fungal component to amphotericin B does not change [45].
Swidergall et al. [46] showed that the surface protein Msb2 produced by *C. albicans* inactivates human antimicrobial protein (AMP), as well as α- and β-defensins. Additionally Msb2 protein binds to daptomycin, the antibiotic used against *S. aureus, Enterococcus faecalis* and *Corynebacterium pseudodiphtheriticum* infections, resulting in the inhibition of its toxicity.

In the oral cavity, the presence of high molecular weight polypeptides on the bacterial cell surface of *C. albicans* allows it to adhere to biofilms formed by streptococci, especially *S. gordonii*. The inactivation of genes encoding cshA and cshB, as well as adhesin sspA and sspB, reduces the adhesion of fungal cells by up to 40–79% [24]. Ricker et al. [47] observe that the biomass of *S. gordonii* increases significantly in a mixed biofilm compared to a one-species biofilm, while the biomass of *C. albicans* does not change. Both the growth of the bacteria and the biofilm are associated with the production of glucosyltransferase (GtfG) after contact with fungal cells. *C. albicans* stimulates the production of GtfG, either directly, by influencing GtfG gene expression, or indirectly, either by induction of the regulatory rgg gene, or changing the environment needed for the activation of the enzyme [47]. Conversely, in a mixed culture of planktonic cells, fungi do not stimulate the proliferation of streptococci, despite the apparent co-aggregation [26].

Each cell produces species-specific and universal-interspecies signals that can regulate the expression of specific genes or change the cellular structure of the recipient. Molecules secreted by *C. albicans* inhibit the motility of *P. aeruginosa*, which may lead to the formation of a bacterial biofilm, or increase its virulence by stimulating phenazine production. One such molecule is farnesol, which reduces bacterial activity by phenazine production. One such molecule is farnesol, which reduces bacterial activity by phenazine production. Additionally, Msb2 protein binds to daptomycin, the antibiotic used against *S. aureus, Enterococcus faecalis* and *Corynebacterium pseudodiphtheriticum* infections, resulting in the inhibition of its toxicity.

**The use of the phenomenon of bacteria–fungi interaction in the technology**

Gram-positive bacteria are often used in food production to convert substrates to products more easily absorbed by the human organism by lactic acid fermentation. The production of dairy products, silage, and some meats is based on the use of such bacteria genera as *Lactobacillus, Lactococcus, Bifidobacterium* and *Propionibacterium*. This activity not only causes the decomposition of high molecular weight organic compounds to simple components which are easily absorbed by the intestinal mucous membrane, but also favors the preservation of the food and prevents the development of species that cause spoilage. Research has shown that the phenyllactic acid produced by *Lactobacillus* sp. is one of the factor responsible for inhibiting the development of a lot of *Penicillium, Fusarium* and *Aspergillus* species. *P. brevicompactum* has been found to inhibit fungal growth by up to 82%, while *P. chrysogenum, P. verrucosum, Aspergillus ochraceus* and *A. terreus* inhibit growth by around 50% [51]. The occurrence of seven linear peptides and two antifungal diketopiperazines with antifungal properties has been detected in *Propionibacterium* species used in dairy products. Cyclic cyclo(L-Phe-L-Pro) and cyclo(L-Ile-L-Pro) inhibit the growth of *Aspergillus fumigatus* and *Rhodotorula mucilaginosa* at a minimum concentration of 20mg/ml [52].

In a rat model, the levels of tumor necrosis factor – and lipid peroxidation during treatment of colitis with a combination of *L. casei* and *Saccharomyces boulardii* were found to be 1/3 of those found after treatment with *L. casei* alone, and the myeloperoxidase content was halved by combination treatment. In rats treated without probiotics, these parameters are 2-3 times higher [53]. The use of *S. boulardii* during the treatment of *Helicobacter pylori*...
pylori infection in children results in the eradication of bacteria in 12%, while the administration of L. acidophilus in 6.5% of cases [54].

Conclusions

The coexistence of fungi and bacteria in cases of systemic infections is a significant diagnostic and therapeutic problem, and the human immune system reacts differently, depending on the pathogen. In cases of respiratory bacterial infections, neutrophils and the cellular response of the TH1 type cells producing interferon-γ are activated. During mucus production and candidosis, eosinophils and TH2 lymphocytes producing interleukin-4 (IL-4), IL-5 and IL-13 are stimulated. However, the response to a mixed bacterial and fungal infection is similar to that elicited by a bacterial infection [35]. During such a co-invasion of bacteria and fungi, the fungus has been found to have increased virulence, which is believed to be related to the presence of a strong bacterial antigen, peptidoglycan, which can circulate in the blood in the form of muramyl dipeptides. It promotes the conversion of the cells of C. albicans into pseudohyphae via activation of the adenylate cyclase Cyr1p pathway. Peptidoglycan may be derived from pathogenic bacteria, but can also constitute the cell walls of commensals [55].

Numerous publications exist concerning the relationship between microorganisms belonging to different ecological groups, the majority of which concern the interaction between macro-organisms and potential pathogens, or the synergistic relationship between parasitic species. However, there is still too little information concerning the role of natural microbiota in maintaining homeostasis and the relationships between particular species inhabiting the human organism. It is very important to know the nature of the interaction between the microorganisms not growing in culture, both pathogens and those which account for the major part of the commensals colonizing the human organism. A detailed knowledge and understanding of the taxonomic structure and role of the natural microbiota in the pathogenesis of bacterial and fungal infections would contribute to the development of newer, more effective antimicrobial therapies and methods of prevention.

References

Cross-kingdom interactions: Candida albicans


