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THE ROLE OF RESIDENT BACTERIAL-FUNGAL INTERACTIONS IN BIOFILM FORMATION DURING WOUND INFECTIONS: DOES BIOFILM FORMATION IN ECOLOGICAL NICHES CONTRIBUTE TO NORMAL FUNCTIONING IN VERTEBRATE MAMMALS?

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Abstract

Recent discussions have focused on the distribution of opportunistic-pathogenic and pathogenic microorganisms that migrate from their biological ecological niches to internal organs and tissues under pathological conditions. Resident gram-negative and gram-positive microorganisms colonize soft tissues, providing optimal conditions for their persistence. Apparently, a similar migration process occurs with resident pathogenic and opportunistic-pathogenic fungi. Resident microorganisms persisting in the soft tissues of wounds begin to form new structures, so called biofilms, which foster new functional interactions between bacteria and fungi. Simultaneously, the role and relative proportion of biofilm-forming microorganisms in the wound inflammatory process have not yet been fully established. Fungi within the biofilm, through their mycelia and pseudohyphae, provide an optimal surface for the adhesion of resident bacteria.

Such an interaction between bacteria and fungi, through biofilm formation, can be realized in three ways under pathological conditions: 1) By simultaneously activating the pathogenic potentials of both fungi and bacteria, 2) By activating only one type of microorganism, while preserving the principle of commensalism with others. 3) By activating only one type of resident microorganisms while inhibiting the activity of another.

Apparently, the formation of biofilms enhances the pathogenic potentials of both resident bacteria and fungi simultaneously, which has a negative effect on the nature and progression of the wound process, especially when it becomes chronic.

Our previous studies have shown that many resident-pathogenic bacteria, including E. coli, play an active role in maintaining immune homeostasis, cardiovascular activity and gastrointestinal function under normal conditions by modulating the production of biologically active factors with immunomodulatory, endocrine-stimulating and cardiostimulating effects.

We believe that the activity of resident opportunistic-pathogenic bacteria in a healthy organism follows the only evolutionarily justified mechanism: the maintenance of their existence by utilizing the energy resources of the macroorganism, while simultaneously participating in the activity of integrative systems at all levels of structural organization. In this regard, we pose the following question: Does bacterial-fungal biofilm formation occur in their ecological niches under normal functioning of vertebrate mammalian organisms?

Keywords: *wound, bacteria, fungi, biofilm, bacterial-fungal interactions in normal and pathological conditions.*

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Introduction

The interaction between microorganisms, involving both bacteria and fungi, leads to the formation of unique microstructures referred to as microbiomes. These microbiomes create optimal conditions for the joint activity of microorganisms within the host macroorganism, particularly in case of local or diffuse infectious and inflammatory processes.

Currently, there is no clear differentiation between the structural formations referred to as microbiomes (biofilm). In particular, this concept often refers to bacterial biofilms, which are presented by mono- or polymicrobial formations.

Such bacterial biofilms form aggregates within the macroorganism, embedded in a protective matrix composed of extracellular structures such as proteins and polysaccharides [*Vestby L et al., 2020; Nesse L et al., 2023*]. One aspect of this issue should be clarified. This review focuses on the role of specific intracorporeal microorganisms – bacteria and fungi, that participate in the formation of bacterial-fungal interactions, often referred to as "biofilm". Pathogenic and opportunistic-pathogenic fungi, when proliferating within the macroorganism, create a mesh-like film structure to which pathogenic and opportunistic-pathogenic bacteria adhere. Bacterial adhesion occurs via fungal hyphae that form the mycelium. These bacterial-fungal interactions are collectively known as "biofilms" [*James G et al., 2008; Clinton A, Carter T, 2015; Percival S et al., 2015*].

What is the biological role of bacterial-fungal biofilms in the onset and progression of a wide range of infectious diseases, including wound infections? In the case of the latter, biofilm structures can contribute to the infection process, which may be triggered by various factors: thermal (e.g., burns, frostbite and gunshot wounds), chemical (e.g., exposure to acids, alkalis, toxic products, including poisonous household and military substances) and traumatic (e.g., household and workplace injuries, knife wounds, crush syndrome), and others.

As we have previously noted, mixed bacterial-fungal microflora often persists in wound lesions during the infectious process [*Groll A, Walsh T, 2001; Gnat S et al., 2021; de Hoog S et al., 2024*].

Such regional inflammatory process is characterized by a severe clinical course and is difficult to treat with all known anti-inflammatory, antibacterial and antifungal drugs [*Becker W, 1991; Dowd S et al., 2011; Pfaller M, 2012; Kapoor G et al., 2017; Reygaert WC, 2018; Berman J, Krysan D, 2020; Pruskowski K, 2021*].

Over the past three decades, researchers have focused on identifying the structural and functional relationship between resident bacteria and fungi persisting in wounds.

A significant emphasis has been placed on this issue in relation to the phenomenon of "bacterial translocation" in the diseased organism [*Deitch E, 1994; Sousa L et al., 1996; Adawi D et al., 2001; Demetriades D et al., 1999; Pfalzgzaff A et al., 2018; Zegadlo K et al., 2023*], where opportunistic-pathogenic and pathogenic resident microorganisms leave their ecological niches (e.g., oral cavity, gastrointestinal tract) and begin to colonize new organs and tissues, initiating pathological processes [*Steffen E, Berg R, 1983; Gautreaux M et al., 1994; Sousa C et al., 1996; Wang X et al., 1996; Nikitenko V et al., 2001; Sahakyan K, 2005; James G et al., 2008; Clinton A, Carter T, 2015; Percival S et al., 2015; Zilfyan A, 2016*]. In this context, the wound inflammatory process is not an exception, particularly when not only bacterial microflora but also mixed bacterial-fungal microflora persist in the wound. The presence of a fungal infection significantly exacerbates the wound process, as fungi not only contribute toxicity but, in association with bacteria, often enhance the pathogenic potential of the bacteria.

In our opinion, the concept of the "microbiome", which includes not only bacteria but also fungi, should be considered from a qualitatively new perspective. Under pathological conditions, newly formed bacterial-fungal communities begin to function, establishing a characteristic network, commonly referred to as a "biofilm".

But what is this network? A complex fungal network provides a surface for the adhesion of a wide variety of pathogenic and opportunistic-pathogenic bacteria [*Dowd S et al., 2011; Short B et al., 2023*]. In fact, the biofilm is an optimal structural microobject, where associative relationships between bacteria and fungi are formed, explaining their long-term persistence in pathologically altered lesions.

Unfortunately, to date, aspects related to the potential functioning of such bacterial-fungal interactions under the physiological conditions of vertebrate mammals are not fully understood.

It is possible that associations formed by resident specific bacteria, fungi and archaea have a beneficial stimulatory effect on various integrative functions, primarily through the targeted synthesis and exocytosis of biologically active substances, particularly those with adaptogenic properties. In our opinion, this aspect of the associative activity of resident microorganisms needs further investigation, as it offers significant perspectives for understanding integrative processes within the interaction of micro- and macroorganisms.

The role of archaea in the vertebrate mammalian organisms remains insufficiently studied. However, even the limited available data suggest that archaea play a significant role in the integrative functions of humans. Thus, it has been established that archaea are involved in methane production during anaerobic respiration. Methanogenic archaea (methanogens) are found in the oral cavity, skin, lungs and gastrointestinal tract. Archaea are present in microbiomes, where they form biofilms with bacteria. In these biofilms, archaea can promote the growth of pathogenic bacteria [*Kuznetsova A, Dukat A, 2022*].

Microbiologists, bacteriologists and infectious disease specialists face considerable challenges in interpreting the nature of biofilms. It remains unclear whether biofilms should be viewed solely as a factor-substrate of the pathogenicity of resident microflora, or if they represent an adaptive process that has evolved in vertebrate mammals, especially humans, enabling microorganisms to adapt to the physiological conditions of the macroorganism.

It is widely believed that biofilm formation occurs primarily in organs and tissues under pathological conditions, particularly in a wide range of somatic diseases, and primarily, infectious bacterial and viral diseases.

From our point of view, the biological purpose of the microbiome should be considered from three perspectives:

From the perspective of biofilm formation, aimed at maintaining favorable conditions for microorganisms during their activity and persistence within the macroorganism, i.e., from a perspective that is beneficial only to the microorganisms.

From the perspective of the production of endogenously active substances by resident microorganisms, which have a modulatory effect. These substances support the activity of various integrative functions, particularly under pathological conditions, facilitating the development of protective and adaptive reactions.

From a mutually beneficial perspective, through which the macroorganism begins to function on a qualitatively new basis – on the principle of mutual interdependence with resident microorganisms.

A few words about the concept of “biofilm” that is frequently used by microbiologists and infectious disease specialists in their scientific studies. The term “biofilm” can also be referred to as “biofilm”.

It is not clear what type of biofilm is being referred to. Is it a biostructure within the body that forms films? Are these artificially created biofilms, treated with various medicinal compositions for the treatment of various diseases? Moreover, the term “biofilm” lacks a principle that would define it as a specific community of microorganisms interacting within the macroorganism in the form of a pellicle.

That is why, we believe that the term “biofilm” by itself is not sufficiently informative, especially when interpreting the processes of persistence of opportunistic-pathogenic and pathogenic microorganisms within the ecological niches of the macroorganism.

In modern microbiology and bacteriology, the concept of the “‘tree of life of microorganisms” is well-established, encompassing bacteria, eukaryotes and archaea. These domains form highly complex interactions within the macroorganism, the overall activity of which remains insufficiently studied to this day.

In our view, the mentioned microbial domains should be defined not as a biofilm, but rather as “bacterial-fungal” and “bacterial-viral interactions”.

The term “interactions” refers to the structural and functional connections between specific microorganisms, which are realized through two mutually exclusive mechanisms.

The first mechanism involves the functioning of these microbial domains based on principles of interrelation and interdependence, aimed at maintaining the activity and persistence of two or three domains.

Through the second mechanism the persistence processes are realized through the activation of only one domain of microorganisms, which, under conditions of increased persistence, suppresses the growth of the other two domains.

It is important to note that in many pathological conditions, microbial interactions primarily function through the first mechanism. Thus, bacterial-fungal resident interactions operate according to this mechanism when, under conditions of fungal reproduction, a biologically active network (a pellicle) is created in the tissues of the macroorganism. This network provides a surface to which bacteria can adhere, thereby creating favorable conditions for their activity and persistence. In this case, the pathogenic potential of bacteria is significantly enhanced.

In our opinion, one important aspect should be noted. The presence of bacterial and fungal communities in the form of a structurally organized biofilm is primarily considered from the perspective of pathology, especially in the context of a wound inflammatory process caused by various provoking factors.

This raises the question: What are the interbacterial-fungal relationships that, in our view, developed in the normal organism during its evolutionary process? This concerns the possible formation of either symbiotic or, contrarily, antagonistic relationships between the macroorganism and resident microorganism.

Undoubtedly, their functional interaction in physiologically established ecological niches (such as the oral cavity, digestive system and possibly the organs of immunogenesis) should only be activated after the structural organization is established, i.e., the formation of a bacterial-fungal matrix, which ensures their positive role in enabling the simultaneous survival of both biosystems (both macro- and micro-).

Unfortunately, similar studies in this sphere have not been conducted. However, we believe that studying the symbiotic activity of bacteria and fungi will significantly advance our understanding of the processes that occur under normal conditions at both the macro- and microbiological levels.

Over the past 70 years, studies have shown that a wide range of resident opportunistic-pathogenic microorganisms (both bacteria and fungi) colonizing the digestive system realize their pathogenic functions due to the presence of aliphatic polyamines – putrescine, spermidine, and spermine, which are essential for their activity and reproduction within the macroorganism [*Merali S, Clarkson A, 1966; Pfaller M et al., 1988; Cervantes Olivares R, 2003; Degreef H, 2008; Gerner E, Meykens F, 2009; Hullar M, 2013; Zilfyan A, et al., 2020; Hakobyan E et al., 2023*].

This circumstance indicates the necessity of significantly correcting the known, ineffective treatment regimens for bacterial and fungal infectious diseases, and, primarily, the wound inflammatory process.

Considering a number of informative studies that have evaluated the biological effectiveness of α-difluoromethylornithine in suppressing polyamine synthesis in bacteria and fungi [*Boyle S et al., 1988; Walters D, 1995; Heby O et al., 2003; Flamigni F et al., 2007; Mounce B et al., 2016; Huang M, 2020*], we believe that further studies should be conducted using α-difluoromethylornithine and/or its analogs (such as the widely used commercial drug "Eflornithine").

Moreover, in the process of palliative wound treatment, we propose using a polyamine-free or polyamine-deficient diet. A recommended list of suitable food products can be found in our previous studies [*Avagyan S et al., 2023*].

These therapeutic and preventive measures should only be implemented following a thorough bacteriological analysis, which will result in polyamine-containing pathogenic and/or opportunistic bacteria and fungi isolated from the wound (and possibly from blood and urine)."

In conclusion, I believe it is both appropriate and, perhaps, even necessary to share several of our considerations regarding the biological significance of resident (i.e. intracorporeal) microorganisms that persist in ecological niches, not only under pathological conditions but also during the normal functioning of our body.

For many years, it has been believed that microorganisms found in human organs and tissues are primarily pathogenic for humans, responsible for a wide range of infectious diseases. Many infectious diseases, especially in the Middle Ages, resulted in fatal outcomes for humans. A similar situation occurred when humans faced zoonotic infectious diseases. In many cases, the same pathogens were harmful to both humans and animals. Massive fatal outcomes were observed in diseases such as leprosy, plague, anthrax, tuberculosis and diphtheria. Often, the widespread nature of these infectious diseases was expressed in the form of epidemics and pandemics.

It never occurred to our ancestors, both ancient and modern, that the bacteria, viruses and fungi living in our bodies, under normal physiological conditions, perform functions that are fundamentally different from those described by many infectious disease specialists, immunologists and pathologists when interpreting the etiology of various infectious diseases. Currently, we believe that scientists, especially those working in various spheres of medicine and biology, should adopt an objectively justified approach based on a single fundamental principle of development of macro- and microorganisms: the evolutionary approach. This perspective highlights the long-established relationship between the macroorganism and the microorganisms living in it. Over centuries, this relationship has evolved into a mutually beneficial one, benefiting both the human and the resident (intracorporeal) microorganisms.

The maintenance of symbiotic relationships between the macroorganism and its resident microorganisms was supported by mutually beneficial functions. On one hand, the integrative functions of the macroorganism are essential for its survival, while, on the other, the participation of intracorporeal resident microorganisms in these functions plays a crucial role in the proper functioning of various organs and systems. Unfortunately, it was only in the last two centuries that modern scientists began to embrace this perspective. During this period, informative data demonstrated that resident microorganisms, through their activity, produce a wide spectrum of biologically active substances of diverse natures. These substances have a profound impact on many physiological functions, including those of the immune, nervous, endocrine and cardiovascular systems. The synthesis of these endogenously active compounds is essential for maintaining the functional activity of integrative systems while also supporting the survival of resident microorganisms within the host organism [*Zilfyan A, 2016*].

A well-founded hypothesis by Professor Aleksanyan A.B., an academician of the Academy of Medical Sciences of the former USSR, which is presented to colleagues in a strictly authorial version: “The diphtheria microbe, when in the unusual conditions of an immune (vaccinated) organism, loses its aggressive properties. As a result of changes and the emergence of new conditions for the existence of the diphtheria pathogen, now it’s the time when its pathogenic nature is transforming towards saprophytization, in other words, into a harmless state for children [*Aleksanyan A, 1957*].

In our opinion, the microbe-host relationship, under normal conditions of the organism’s activity, should be based on at least two fundamental principles:

The principle of synergistic relationships among resident microorganisms within a single interaction. Inter-associative connections between different microorganisms, such as bacteria and fungi, are possible, particularly within various target organs where they persist.

The development of the infectious process is due to the disruption of the “dynamic” equilibrium between the evolutionarily established relationships in various microbial interactions.

The principle of biological expediency in the “coexistence” of microbial interactions and the host organism, developed through evolutionary processes, involves micro- and macro-structures, optimized for the growth and vitality of microorganisms, while also supporting the integrative functions of the host organism.

Ten years ago, one of the co-authors of this publication proposed the hypothesis that “intracorporeal interactions of resident microorganisms should be considered as an independent system in the integrative activity of the mammalian organism” [*Zilfyan A, 2016*].

The problem of long-term persistence of opportunistic-pathogenic and pathogenic bacteria and fungi in a macroorganism remains a topic of special study. Under pathological conditions, resident microorganisms initiate interactions within their ecological niches to ensure their survival utilizing the host’s energy resources. We propose that pathogenic and opportunistic-pathogenic fungi, persisting in the same ecological niches, not only contribute to the development of infectious processes but also carry out their functional activity under normal conditions through the formation of their hyphae (mycelium and pseudomycelium).

There is no alternative method for resident fungi to adhere to the tissues that form the ecological niches within the host's organism. Under normal conditions, intracorporeal resident fungi seem to function based on the unique features of their structural organization – creating mesh-like microstructures. In the same ecological niches and under the same conditions of normal functioning, intracorporeal resident opportunistic-pathogenic and pathogenic bacteria perform their multifaceted physiological functions.

In our view, when resident bacteria "interact" with the fungal network within each specific ecological niches, bacterial-fungal interactions, i.e., "biofilms", are formed.

A completely different situation arises under pathological conditions, when a local and/or diffuse infectious process occurs, triggered by a variety of provoking factors. In such cases, the virulent potentials of not only pathogenic but also opportunistic-pathogenic bacteria and fungi are significantly activated.

In our view, a structural and functional rearrangement of biofilms occurs, with their components, as their virulent potentials increase, beginning to exert an alternative (damaging) effect on somatic cells and the interterritorial matrix, both at the site of the wound and on the cellular and extracellular structures of internal organs. In this case, the infection spreads through the penetration of microorganisms into internal organs via hematogenous and lymphogenous pathways.

Moreover, it is not excluded that other virulent bacteria, migrating from different ecological niches within the macroorganism, may adhere to the surface of the fungal reticular structures.

Given this, we pose a very legitimate question, the answer to which would allow us to characterize, from a qualitatively new perspective, the evolutionarily formed "mutually beneficial" symbiotic relationships between the macroorganism and the intracorporeal (resident) bacterial-fungal interactions.

More specifically, the question is as follows: Is the principle of "biofilm" formation in ecological niches involved under the conditions of normal functioning of the macroorganism?

Our answer to the question we posed can be found in our monograph published in 2016: "The System of Intracorporeal Resident Microorganisms Involved in the Normal Functioning of the Organism" [*Zilfyan A, 2016*]. This definition should be understood as the associative activity of resident microorganisms (bacteria, fungi, and viruses) that persist in the host's ecological niches. These microorganisms function in a healthy organism through a mechanism that is evolutionarily fixed and well-justified: they maintain the host's existence by utilizing energy resources of the macroorganism, while simultaneously participating in the physiological activity of integrative systems at all levels of their structural organization.

Conclusion

In the organism of vertebrate mammals, under pathological conditions, especially in case of a chronic infectious process, biofilms of varying structural organization begin to form, depending on the types of resident bacteria and fungi. While bacterial biofilms have been widely described, fungal biofilms are less studied, and bacterial-fungal interactions in pathological lesions are relatively underexplored. However, this distinction is somewhat subjective, as mixed bacterial-fungal interactions often persist in pathological lesions, especially in newly formed ecological niches. Both resident opportunistic and pathogenic bacteria, as well as fungi, participate simultaneously in biofilm formation. The proportion of bacteria and fungi within the biofilm matrix can vary widely, depending on several factors, including the nature of the infectious process, its chronicity and the degree of immune suppression of the organism. The state of the biocenosis formed by resident bacteria and fungi within an ecological niche is largely determined by the specific relationships formed between them.

The formation of biofilms and their functional dynamics in pathological conditions depend on several factors, including:

The taxonomic characteristics of the specific bacteria and fungi.

The symbiotic and antagonistic relationships persisting in bacterial ecological niches.

The symbiotic and antagonistic relationships persisting in fungal ecological niches.

The virulence potentials acquired by both bacteria and fungi as they persist within a single ecological niche.

The emergence of bacterial translocation, wherein bacteria persisting in one ecological niche begin to migrate and colonize new ecological niches within the macroorganism.

As previously noted, when a matrix is formed solely by bacteria, it is composed of the products of their metabolic activities (and potentially their decay), such as proteins, glycoproteins, extracellular (free) DNA, and other substances. The structure of the bacterial matrix is highly variable, depending on the taxonomic and virulent potentials of various bacteria. It depends on the nature and intensity of the catabolic products they produce that facilitate the adhesion of bacteria to the matrix.

It is noteworthy that a range of advanced researchers have tried to characterize the specific stages of bacterial biofilm formation, often referred to as "biofilms" [*Carniello V et al., 2018*], which were divided into four stages:

Transfer of bacterial mass to the surface.

Reversible bacterial adhesion. This stage is characterized by weak desmoplastic connections between the bacterial matrix and surrounding somatic cells, as well as the extracellular environment.

The stage of irreversible adhesion, characterized by more intense production of bacterial biofilm material for matrix formation, leads to the development of more pronounced desmoplastic processes between the resident bacteria adhered to the matrix surface and the peripherally oriented cellular and extracellular structures of the host organism.

Deformation of the bacterial cell wall and acquisition of emergent (atypical) properties.

It's interesting what the authors mean by this dynamic process of bacterial biofilm formation by using the terms "deformation" and "emergent properties of bacteria".

Both expressions do not fully capture the structural and functional changes that bacteria undergo during this stage. Regarding "deformation", it is unlikely that bacteria persisting in biofilms undergo "mass" destruction of their cell walls, leading to general deformations of the cytoplasmic membrane at the initial stages of biofilm development. It is unlikely that bacteria forming biofilms can acquire new properties that are not characteristic of them. In this context, we believe that the focus is on the enhancement or, conversely, the weakening of the virulent potential of each bacterial associate, as well as the adhesive capacity of the outer membranes of bacterial cells, which enable these bacteria to move not only within the matrix but also migrate to neighboring ecological niches.

It is possible that this migration process, where bacteria leave one biofilm and colonize new areas, might represent the beginning of bacterial translocation. Unfortunately, this process, through which bacteria colonize new ecological niches by migrating from established biofilms, has not been thoroughly studied before the publication of this article.

A similar gradation of reversible and irreversible adhesion processes has also been described in relation to the formation of biofilms (matrices) involving resident pathogenic fungi [*Gaffarova A, Khaytovich A, 2017; Abdulkair W, 2018; Enokaeva O et al., 2021*].

As early as 30 years ago, some leading scientists – microbiologists and bacteriologists expressed a prophetic thought for that time: "Even monomorphic bacteria within a single colony can differentiate into cells of different types, and that is most important, they form multicellular structures with highly organized architectures; the associative activity of such bacteria is subject to chronological control" [*Shapiro J, 1988*].

Moreover, there is an opinion that certain bacterial interactions exhibit specific skills characteristic of highly organized organisms. In the process of colonizing a macroorganism, some bacterial populations facilitate the advancement of the entire microbial community through biological substrates, while others ensure the functional activity within the macroorganism (e.g., production of biologically active substances with physiological and alterational effects, or by acquiring virulence properties). Some populations also provide the adhesive properties necessary for the persistence of other populations within the macroorganism's ecological niches.

In our view, the specific populations of bacteria that undergo adhesion are precisely those that function within the host organism by forming biofilms, i.e. biofilms.

As a result of analyzing the literary sources, it becomes evident that the structure of the matrix on which resident bacteria and fungi adhere is not straightforward, as it depends on the specific types of resident microorganisms involved in the formation of biofilms.

In cases where only bacteria participate in the formation of the matrix, it is composed of their metabolic and degradation products (such as proteins, polysaccharides and free DNA). However, when both resident bacteria and fungi are involved in biofilm formation, the matrix structure becomes more complex. Thus, the statement that the hyphae of resident fungi, due to their anatomical features, merely serve as a substrate on which resident bacteria adhere (i.e., undergo adhesion) appears somewhat unjustified. That's why, the focus should not only be on the products of bacterial catabolism, as resident fungi themselves possess significant synthetic potential, particularly in producing a wide range of biologically active compounds, which also play a direct role in biofilm formation.

According to our hypothesis, under normal physiological conditions, opportunistic-pathogenic and pathogenic resident bacteria and fungi function within the biological ecological niches of the macroorganism. If our hypothesis is valid, then the structure of resident bacterial-fungal biofilms in a healthy organism should be markedly different from those formed during pathological conditions.

Thus, under normal conditions, the structural and functional organization of bacterial-fungal biofilms must adhere to the following criteria:

Firstly, the ecological niches in which resident bacteria and fungi collectively form biofilms must be strictly determined.

Secondly, only the bacterial-fungal interactions characteristic of each specific ecological niche should persist within it.

Thirdly, the functional activity of such ecological niches, in which resident bacteria and fungi persist, is selectively directed toward supporting many integrative functions of the macroorganism through the synthesis of a range of physiologically active substances that play a direct role in regulating organs and systems. Apparently, such synchronized activity of resident intermicrobial interactions is embedded in the evolutionary development of macro- and microorganisms, functioning on the principles of interdependence.

In pathological conditions, bacterial-fungal interactions in the macroorganism exhibit distinct structural and functional characteristics that differ significantly from those present during normal conditions. These interactions must meet the following criteria:

Firstly, the types of bacteria and fungi significantly differ from those that persist in the ecological niches under normal functioning conditions of the macroorganism.

Secondly, such resident microorganisms exhibit pronounced virulent properties.

Thirdly, high-virulence strains of microorganisms begin to function not only in evolutionarily formed ecological niches but also as the pathological process progresses.

Fourthly, in such a situation, the "phenomenon of bacterial translocation" starts to function, whereby resident microorganisms start migrating from their ecological niches and colonizing new ones.

Fifthly, the acquisition of new virulent potential largely depends on the production of biologically active substances, particularly with toxic effects, by resident bacteria and fungi, which has a profoundly negative impact on the course of pathological processes of various origins, including both infectious and non-infectious etiologies.

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