POINT OF VIEW

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ON THE POSSIBLE MECHANISMS OF MICROBIOME INVOLVEMENT IN INDUCTION OF MALIGNANCY

The close coexistence of organisms of different biological species is one of the leading principles of the organization of living matter. The interaction of microbial biofilms with adjacent tissues of the host deserves special attention. The article raises controversial issues related to the possible malignant effect of microbial biofilms.

Keywords: malignancy, tumor, biofilms, microbial resistance.

Arthur Kornberg once noted that the world we live in is inhabited mainly by microorganisms with extremely rare inclusions of multicellular organisms [1]. It is difficult to disagree with this, but we should not forget that all multicellular organisms are colonized by microorganisms that have complex relationships both with each other and with the cells of the host organism [2, 3]. A classic example of such symbiosis is the colonization of the stomach and intestines by bacteria involved in food digestion. At the same time, some of the bacteria present in multicellular organisms do not bring any benefit to the host at first glance, but upon closer inspection protect the body from colonization by other, often pathogenic, bacteria.

The dominant form of microorganisms' existence are biofilms (BFs) [4]. According to the generally accepted definition, BF is an aggregate of microorganisms, in which cells are fixed among themselves and to an insoluble surface due to the incorporation into the matrix of extracellular polymeric substance (EPS), synthesized by the bacterial cells themselves [5]. Usually, BFs are formed by various microorganisms with complex, not always mutually beneficial, relationships with each other [4, 6, 7].

BFs exist both in a form fixed on an insoluble surface and in a mobile form not associated with any substrate. EPS is a highly organized substance containing protein, carbohydrate, lipid, and nucleic components. Carbohydrates are involved in ensuring proper hydration of the biofilm and its permeability to substances necessary for microorganisms. The insoluble component of EPS formed by protein fibrils ensures mutual adhesion of microorganisms to each other and to the adjacent tissues [8]. It covalently binds various enzymes secreted by microorganisms or released upon their death. This turns EPS into a kind of an external digestive sys-

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tem that transforms the decay products of dead microorganisms and substances coming from the environment into a form that is acceptable for cells [5]. The composition of EPS includes nucleic components of dead microorganisms, which play a role of a protective filter, an adhesive component, and a source of phosphorus. An important function of the extracellular nucleic components of BFs is to ensure the horizontal transfer of genes. As a result of the horizontal transfer of genes, the formation of chimeric microorganisms occurs, which to a greater or lesser extent correspond to the conditions of the surrounding environment.

The permanent death of a fraction of the cells and remodeling of EPS is an integral condition for the existence and development of BFs [9]. Microorganisms in the composition of BFs are significantly inferior to the free forms in the rate of reproduction. However, due to the increased resistance to the influence of various negative environmental factors, BFs are the dominant form of existence of microorganisms.

Upon the exposure to the adverse external factors, a certain part of cells dies, while others retain viability in an active or persistent state [10—12]. Mass death of the bacterial cells will lead to a sharp increase in the amount of cellular products in the intercellular environment, in particular, proteins and nucleic acids. The released proteins and peptides become structurally destabilized, which contributes to their incorporation into the outer cell membranes of BF cells. This process has a parametabolic character, requiring neither enzymatic regulation nor the supply of external energy [13]. The formation of such inclusions has two important consequences. First of all, the insertion of a destabilized peptide chain into the phospholipid bilayer of the cell membrane occurs according to certain rules. This process includes sorption of the peptide chain on the surface of the membrane, its alpha-helixization, embedding of the formed helix into the phospholipid bilayer, association of similar inclusions with each other and their rearrangement into beta-folded structures that penetrate the phospholipid bilayer of the cell membrane [14].

Such inclusions tend to associate both with each other and with integral proteins of the cell membrane, which disrupts the functioning of the latter. Such interactions are involved in various pathological processes [15]. At the same time, β-structured protein aggregates have another feature that remains underestimated in terms of their influence on the properties of individual cells and their associates. Due to the peculiarities of the structure, β-structured protein aggregates are electrically conductive [16]. Because of this, β-structured protein fibrils of the EPS can not only be scaffolds of BFs but also play a significant role in the formation of the signaling system in quorum sensing [17, 18]. In addition, the incorporation of destabilized proteins and peptides into the cell membrane occurs according to the "positive-inside" rule [19]. According to this rule, the unbalanced positively charged amino acid residues are oriented inside the cell, and the balanced pairs of positively and negatively charged amino acids are exposed on the surface.

All this leads to local or systemic depolarization of the outer cell membrane. The barrier function is the most important role, which cell membranes play. An integral circumstance of the normal functioning of the membrane is the asymmetry of its structure and the presence of an electrostatic field gradient between the outer and inner phospholipid layers. Support of this gradient is provided by numerous cell systems. When the cell dies, this gradient disappears, and the permeability of the outer membrane increases sharply [20]. The shunting of the phospholipid bilayer by electrically conductive inclusions changes the barrier function of membranes. Given the high level of structuring of membranes, this does not necessarily involve the complete destruction of the electrostatic gradient: the modification may be partial and confined to a certain area. It is known that microorganisms in a BF intensively absorb nanosized particles of most diverse nature. In this regard, they differ sharply from microorganisms in a free (unbind) form. A dramatic increase in the permeability of the outer membranes of bacterial cells is observed.

These processes along with the constant selection of viable forms ensure the transition of the BF to a higher resistant level. The formation of resistance of the pathogenic microorganisms to the action of medicinal products has long turned into a complex medical and social problem, which significantly complicates and sometimes precludes effective treatment [21]. No less indicative is the development of drug resistance in BFs intoxicated by heavy metal ions [22]. The question of the influence of formation of microbial resistance on the adjacent cells of the host deserves special attention.

All mentioned above processes intensify significantly under the influence of the adverse factors and

during the formation of microbial resistance. The embedding of the individual components of EPS in adjacent tissues of the host affecting their function have been shown [23]. The destructive effect of BFs, mediated by the secretion of certain enzymes, is known as a cause of chronic inflammation [24]. All of this may contribute to malignization of the tissues of the host. The above considerations allow us to raise the question of the malignant effect of microbial resistance formation on adjacent tissues.

As already noted, the intensity of metabolism of microorganisms significantly exceeds that of cells of multicellular organism, especially under the influence of adverse factors. This creates the prerequisites for the saturation of the surface layer of adjacent tissues with the products of BF decay in amounts exceeding the capabilities of the clearance systems of multicellular organisms. Accumulation of the surface layer of adjacent tissues with proteins of altered structure and the nucleic components of the dead BF cells provides the latter with malignant properties. On the one hand, the formation of mutated cells in the adjacent layer and their subsequent selection can occur similarly to the mechanism of formation of resistant biofilms. On the other hand, the saturation of cell membranes with protein inclusions oriented by the "positive-inside" rule creates prerequisites for the sorption of components of the fibrinolytic system, their activation, and the launch of the cascade of non-functional proteolysis characteristics of cancer cells [25]. All this is only a small portion of the consequences of the intensive accumulation of the decay products of microorganisms in the adjacent tissues [13].

Known data on the factors determining the risk of developing cancer, in particular in the ENT organs support the stated considerations. The leading risk factors for the development of cancer of the mucous membrane of the oral cavity, larynx, and pharynx include smoking and consumption of strong alcoholic beverages, hot spices, and hot food [26, 27]. The obligate biofilms located on the mucous membrane of these organs are the first to be affected by the factors listed above. An access to the adjacent tissues of the substances produced during the formation of microbial resistance can cause degenerative changes in adjacent tissues. Characteristically, the leading risk factors for cancer of the ENT organs cause leukoplakia, papillomatosis, chronic ulcers, and atrophic changes [26, 27]. One of the known negative factors inducing the development of microbial resistance is a change in the acidity of the environment. Therefore, it is not surprising that laryngopharyngeal reflux not only determines the occurrence of polyps and granulomas of the larynx but is also considered a risk factor for the development of laryngeal cancer [28]. The impact of poor-quality prostheses is one of the risk factors for oral mucosal cancer [26]. Ultra-low amounts of the components of a low-quality implant may be insignificant for body tissues but still sufficient to initiate the formation of BF resistance with subsequent regeneration of adjacent tissues.

The given considerations are a generalization of the known data on the regularities of the functioning of BFs, their reaction to negative environmental factors, and the possible influence of the substances formed in this process on the adjacent tissues of a multicellular organism. Substances intensively produced during the formation of microbial resistance are able to affect the cells of adjacent tissues and induce their regeneration up to malignization [29]. This allows us to substantiate the assumption about the role of BFs as mediators of the influence of adverse factors and inducers of regeneration and malignization in adjacent tissues.

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ЩОДО МОЖЛИВИХ МЕХАНІЗМІВ УЧАСТІ МІКРОБІОМУ В ІНДУКЦІЇ ЗЛОЯКІСНОСТІ

Тісне співіснування організмів різних біологічних видів є одним із провідних принципів існування живої матерії. Взаємодія мікробних біоплівок із прилеглими тканинами макроорганізму заслуговує на особливу увагу. Наявні дані дозволяють обґрунтувати припущення про можливий малігнізуючий вплив мікробних біоплівок на прилеглі тканини під час розвитку резистентності до несприятливих для мікроорганізмів факторів навколишнього середовища.

Ключові слова: злоякісність, пухлини, біоплівки, мікробна резистентність.