MALIGNIZATION AS A CONSEQUENCE OF THE FORMATION OF MICROBIAL RESISTANCE

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Summary. The ability of microorganisms to form multicellular three-dimensional associates (biofilms) increases significantly their resistance to the influence of negative environmental factors. One of the manifestations of this ability is the development of drug resistance, which leads to a decrease in the effectiveness of drugs and significantly complicates the treatment of the corresponding diseases. Despite the unabated interest in this extremely undesirable phenomenon, there is no generally accepted explanation of the mechanisms of resistance development. At the same time, the generalization of data on the properties of biofilms allows us to get closer to the understanding of this process, but also to substantiate the proposition about its negative impact on adjacent tissues.

Key words: biofilms, tumor, malignancy, microbial resistance
Extracellular polymeric substance (EPS) is an integral component of various biofilms (BFs). It connects individual microorganisms and ensures the integrity of the BF [1]. EPS is a highly organized substance containing protein, carbohydrate, lipid and nucleic components. Carbohydrates are involved in ensuring proper hydration of the BF and its permeability to substances necessary for microorganisms [2]. The insoluble component of EPS formed by protein fibrils ensures mutual adhesion of microorganisms to each other and to adjacent tissues [3]. It conjugates covalently various enzymes secreted by microorganisms or released upon their death. This turns the EPS into a kind of external digestive system that transforms the decay products of dead microorganisms and substances coming from the environment into a form that is acceptable for cells [2]. The composition of EPS also includes nucleic components of dead microorganisms, which are traditionally assigned the role of a kind of protective filter, an adhesive component and a source of phosphorus [4,5]. However, an equally important function of the extracellular nucleic components of BFs is to ensure the horizontal transfer of genes. Usually, BF are formed by various microorganisms that are in close, not always mutually beneficial, relationships with each other [6,7]. 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 [2,8,9]. Some of the cells formed during the division of such mutants become unfit for life, others acquire new properties, and a certain part falls into a persistent state. All these processes provide phenotypic changes of BF cells and their differentiation according to their location in one or another part of it. At the same time, the permanent death of part of the cells and re-modeling of the EPS is an integral condition for the existence and development of BF. It is this that provides the material both for the nutrition of surviving microorganisms and for the development of EPS. The latter, in turn, increases the protection of cells, and therefore the survival of the cellular society as a whole [2].

What changes does the BF undergo under the influence of an external adverse factor, not necessarily an antibiotic? The death of a certain part of cells will lead to a sharp increase in the number of their decay products in the intercellular environment, in particular, proteins and nucleic acids. At the same time, the protein components undergo additional cleavage by free and immobilized EPS proteinases. Similar proteins and peptides become structurally destabilized, which provides them with the ability to incorporate into the outer cell membranes of BF cells [10]. This process has a regular character and creates prerequisites for the depolarization of the outer cell membrane and, as a result, for the increase in its permeability. The latter, in the presence of extracellular nucleic components in the environment, becomes a sufficient prerequisite for the development of mutational processes. All of the above, together with the constant selection of more or less viable forms, ensures the transition of the BF to a higher, resistant level. At the same time, it is worth noting that resistance has a fairly wide range of protection and ensures the survival of the cell society not under the influence of the initial adverse factor only, but also various others. This can probably explain the formation of polyresistant forms of infectious agents [5]. Diseases caused by them are extremely difficult to treat with antibiotics. No less revealing is the example of the development of antibiotic resistance in biofilms that were formed under the negative influence of copper ions [11]. The continuous dying of part of the cells becomes a necessary
condition for the existence of a resistant BF [5]. At the same time, the continuous process of formation and degradation of EPS undergoes significant changes in response to changes in the surrounding environment [2].

There is a certain analogy in the structure and functioning of multicellular associates of microorganisms and cells of malignant tumors [13]. The intercellular polymeric substance of BF and the stroma of malignant tumors are similar in composition and play an important role in the functioning of the corresponding associates. Both types of associates form significant amounts of extracellular protein and nucleic components. The intercellular worm of both types of associates contains significant amounts of hydrolytic enzymes. Cellular components of both types are characterized by increased permeability to extracellular substances, in particular nanoparticles. Cells of both BF and malignant tumors are characterized by wide genetic diversity even within the same biofilm or tumor. And, in addition, malignant neoplasms also have the ability to acquire resistance to the action of cytostatics [10].

Such an analogy allows us to raise the question of the possible influence of BF, their resistant forms primarily, on adjacent tissues. At the same time, the main attention is paid to the destructive action of BF, which is mediated by the secretion of certain enzymes [12]. This action is a recognized cause of chronic inflammatory process [5]. However, the given analogy in the functioning of multicellular associates of malignant neoplasms and BF allows us to raise the question of the possible malignant effect of the latter.

In terms of the intensity of metabolism, single-celled organisms surpass significantly multicellular cells. Individual components of EPS are able to integrate into adjacent tissues and significantly influence their functioning [14]. That is, there are prerequisites for saturating the surface layer of adjacent tissues with BF decay products in quantities exceeding the capabilities of the clearance systems of multicellular organisms. This makes the resistant form of BF a possible malignant factor that saturates the surface layer of adjacent tissues with proteins with a broken structure and nucleic components of dead cells. The formation of mutated cells and their subsequent selection occurs similarly to the mechanism of formation of resistant biofilms. In addition, the incorporation of destabilized proteins into the outer membrane of cells occurs according to the "positive-inside" rule, according to which unbalanced positively charged amino acid residues are oriented inside the cell, and balanced pairs of positively and negatively charged amino acids are exposed on the surface of the cell (Fig. 1).

![Fig. 1. Scheme of incorporation of an extracellular peptide into a polarized cell membrane according to the "positive-inside" rule](image-url)
The latter are connected effectively by components of the fibrinolytic system with further development of non-functional proteolysis, which is characteristic of malignant neoplasms [15].

Usually, BF\textsubscript{s} are formed at the interface of phases. It is likely that this boundary is perceived by microorganisms as a primary stress factor that stimulates mutual adhesion of microorganisms with subsequent formation and development of a BF. A huge number of research works are devoted to these processes, but those that take place in the formed BF under the action of an additional damaging factor deserve no less attention. The processes of formation of resistance will lead to the arrival of substances capable of inducing the process of malignancy to the adjacent tissues. In this regard, the factors determining the risk of developing oncological diseases of the ENT organs are very indicative in this regard. Thus, the leading risk factors for the development of cancer of the mucous membrane of the oral cavity, larynx, and pharynx include smoking, consumption of strong alcoholic beverages, spicy spices, and hot food [16-18]. Obligate BF\textsubscript{s} of the mucous membrane of these organs are the first to be affected by these factors. The intense influx of substances to the adjacent tissues, which are formed during the formation of microbial resistance, can cause various degenerations of the adjacent tissues. It is characteristic that the leading risk factors for cancer of the ENT organs cause leukoplakia, papillomatosis, chronic ulcers and atrophic changes [16,18]. One of the known negative factors inducing the development of microbial resistance is a change in the acidity [7]. 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 [19]. The impact of poor-quality prostheses is one of the risk factors for oral mucosal cancer [16]. The issue of biocompatibility of implant materials has a pronounced practical significance and is subject to intensive research [20]. The formation of biofilms on the surface of implants and dental prostheses has also been known for a long time and is intensively studied [21]. Unfortunately, the question of the causes of the formation of biofilms, which are qualitatively different from the usual microbiota of the oral cavity, was neglected. Possible differences in the reaction of the components of a multicellular organism and microbial BF\textsubscript{s} to the influence of the components of this or that foreign material deserve attention. Ultra-low amounts of the components of the implant may be insignificant for body tissues, but cause the formation of a resistant BF. In this case, forcing the resistance of the biofilm can cause the regeneration of adjacent tissues.

Unicellular organisms significantly outnumber the cells of multicellular ones in terms of intensity of metabolism and speed of division. Substances that are intensively formed during the formation of microbial resistance are capable of influencing the cells of adjacent tissues and inducing the processes of their regeneration up to malignancy. From such point of view, BF\textsubscript{s} act as mediators of the influence of a negative factor and inducers of regeneration processes of adjacent tissues. This allows us to substantiate the assumption about the mediating role of biofilms in the initiation of the process of oncogenesis.

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