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МЕДИКО-БИОЛОГИЧЕСКИЕ НАУКИ

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БАКТЕРИАЛЬНЫЕ ЭФФЕКТОРЫ ПОВРЕЖДЕНИЙ ДНК В КЛЕТКАХ ОРГАНИЗМА ХОЗЯИНА

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BACTERIAL EFFECTORS OF DAMAGING DNA IN HOST'S CELLS

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Аннотация. На сегодняшний день важно изучение микробиоты, поскольку она оказывает большой эффект на гомеостаз организма хозяина. Микробиота производит мутации в клетках организма хозяина, такие как повреждение ДНК, остановка репарации и т.д. В статье содержится информация о результатах экспериментов, методов влияния микробиоты.

Annotation. Nowadays it is important to study microbiota because it has a big effect on host's homeostasis. Microbiota makes mutations in the cells of the host organism, such as a damage of DNA, delay of reparation etc. The article contains the information about the results of the experiments, methods of microbiota's effect.

Ключевые слова: биологические мутагены, микробиота, бактериальные генотоксины, бактериальные эффекторы повреждений ДНК.

Key words: biological mutagens, microbiota, bacterial genotoxins, bacterial effectors of DNA's damage.

Introduction

There are some factors which cause different mutations of organisms. In general, factors can be physical, chemical and biological. Our organism contains a big amount of bacterium called microbiota. With the help of sequencing the bacterium's genomes have been investigated. Scientists have associated composition of bacterial microflora and type of disease. In fact, not only pathogenic microflora cause mutations but normal too. Examining microbiota, information about bacterial genotoxins and other bacterial effectors-damagers eukaryotes' DNA [1].

Well, **the goal of the research** is to learn about about mutational and damaging effect on host's DNA, observations during experiments and make a conclusion. Actually, the methods of the research consist of observation, experiments.

An influence on DNA of host's target cells is made by different genotoxins. For example, a big role of changing the structure of DNA play typhoid toxin from Salmonella enterica serovar Typhi [1, 2], cytolethal drawling toxin (CDT) from Escherichia coli [1, 3], Aggregatibacter actinomycetemcomitans etc., and, finally, the third one is colibactin from Escherichia coli [1,4].

At first, CDT was found in pathogenic strains of E. coli, which were got from patients with diarhhorea. Well, CDT is a kind of proteins which has got CdtB – analogue of mammals' ferment DNAase. This ferment can split DNA both in the form of plasmid and highly orginised form of eukaryote's DNA. Thus, CDT gets into a core via endocytosis through Golgi stacks and endoplasmic reticulum and then mutates [1, 5].

After delivering CdtB into core of target cells toxin mutates DNA and causes a stop of cell cycle or its death according to its type or amount of toxin. Moreover, experiments showed that a small amount of toxin resulted in a single split during 3-6 hours after intoxication. Next these single splits turn into double. If the amount of toxin is big, there won't be single splits. In fact, the double splits will appear immediately. As a result, genotoxins can lead to inflammation, damaging of tissues, and, therefore, to several forms of cancer [1].

Colibactin is a bacterial DNA-effector which of peptid-polyketide nature. Colibactin needs a close contact with cells of epithelium and the result is inflammation. Like a CDT colibactin activates a ferment DDR and ATM/ATR which lead to stop of cell cycle and, eventually, to cell's aging and death. By the way, these aging cells allocate causing inflammation cytokins, hemokins, factors of cancer's growth [1].

A characteristic feature of genotoxin-producing bacteria is the presence of operons in their genomes that encode the synthesis of these compounds that can damage DNA. However, recent researches in this area have shown that, in addition to genotoxins, there are other bacterial DNA damage effectors in eukaryotic cells. In these cases, mutagenesis in the cells of the host organism is associated with the formation of DNA-reactive metabolites of bacterial activity, generation of radicals, or immune modulation of the cells of the host organism. It should be noted, these bacteria include Helicobacter pylori, Pseudomonas aeruginosa, Enterococcus faecalis, Shigella flexneri, Bacteroides fragilis, Neisseria gonorrhoeae, Listeria monocytogenes, Chlamydia trachomatis, etc.

1. Helicobacter pylori

This gram-negative bacterium colonizes the stomach of almost half of the world's population. In most cases, colonization of H. pylori does not cause symptoms; although only about 20% of preneoplastic changes occur, and in about 2% of cases, infection leads to the development of stomach cancer and lymphoma [1]. Settling on the gastric mucosa, this bacterium causes lifelong inflammation, predisposing to genomic instability and DNA damage.

H. pylori increases the level of gene mutations in the epithelium of the gastric mucosa in patients with chronic gastritis. An increased level of micronuclei in

mucocytes of the mucous membrane of the antrum was found during invasion of H. pylori in patients with chronic gastritis. Thus, with H. pylori infection, the formation of genotoxic products occurs that exceed the normal range characteristic of the inflammatory response in uninfected patients, which leads to a significant increase in the number of mucocytes with cytogenetic disorders. It should be noted that there are results of both experimental and population studies suggesting that H. pylori is also able to induce mutagenesis in mitochondrial DNA, which apparently enhances oxidative stress and promotes the development of gastric cancer.

In conclusion, H. pylori can act on the DNA of the cells of the host body in two independent ways: either directly (the mechanism is unknown), or through inflammation, causing oxidative or nitrosative stress. It can also be said that H. pylori is one of the few bacteria directly causing damage to the DNA of the host cell.

2. Pseudomonas aeruginosa

Another widely known bacterium that can cause direct DNA damage in the cells of the host body is Pseudomonas aeruginosa. Well, this gram-negative conditionally pathogenic bacterium is the causative agent of human nosocomial infections due to the fact that it is particularly easy to infect individuals with weakened immune status, in particular patients with cystic fibrosis or with severe burns [1].

Today the ultimate mechanisms leading to DNA damage due to P. aeruginosa infection are still unknown.

3. Bacteroides fragilis

Some strains of this obligate anaerobic commensal are capable of producing enterotoxin (Bft), which causes acute diarrheal disease, also associated with colorectal cancer [1]. In a single research, B. fragilis was shown to act indirectly, causing high levels of ROS, which in turn damage the DNA of host cells.

4. Enterococcus faecalis

Another common intestinal microorganism is fecal enterococcus. This gram-positive intestinal commensal, which is part of the normal microflora of the human digestive tract, produces extracellular superoxide, as well as ROS derivatives such as hydrogen peroxide and hydroxyl radical. Therefore, infection with E. faecalis can lead to genomic instability in the intestinal cells [1].

5. Shigella flexneri

Shigella Flexner is a gram-negative facultative anaerobic. It affects the epithelium of the colon and rectal zone of a human, causing destructive rectoctolitis, acute gastroenteritis, which is also called shigellosis or bacterial dysentery. It should be noted that a feature of the S. flexneri life cycle is that this bacterium replicates in infected cells, initiating inflammation and tissue destruction. In addition, it was found that S. flexneri inhibits p53 via VirA, contributing to calpain-dependent degradation of p53, which ultimately inhibits apoptosis of infected cells and disrupts p53-dependent activation of DNA reparation. The mechanism of the genotoxic action of S. flexneri remains unclear, however, it serves as a good example of the ability of

bacteria to increase their own survival and ensure replication, avoiding premature death of infected cells of the host body [1].

6. Neisseria gonorrhoeae

Neisser gonococcus causes purulent inflammation of the mucous membranes of the genitourinary system. By infecting epithelial cells, gonococcus acts like Shigella flexneri, affecting the p53 signaling pathway.

P53 inhibition may be the mechanism evolutionarily developed by N. gonorrhoeae to maintain the survival of host cells, despite the presence of DNA damage. Thus, the epithelium of the urogenital tract is a protected niche where gonococci are able to survive and multiply in the cytoplasm of the cells of the host organism, evading extracellular immune responses [1].

7. Listeria monocytogenes

Gram-positive rod-shaped bacteria, one of the most common foodborne pathogens in the world, cause severe infections (listeriosis) in pregnant women and infants with weakened immunity [1].

Like other bacterial DNA effectors, L. monocytogenes infection increases the length of the cell cycle of the host organism without compromising their viability. However, unlike other bacteria that stop the cell cycle, listeria induces a delay in the synthetic phase, facilitating DNA reparation. One of the probable mechanisms of the genotoxic effect of this pathogen may be histone deacetylation using Sirtuin 2 deacetylase. Thus, L. monocytogenes manipulates the eukaryotic genome through a number of mechanisms that promote the survival and replication of this bacterium.

8. Chlamydia trachomatis

Another representative of Chlamydia trachomatis is an obligate intracellular pathogen that is involved in a number of infectious diseases of the genitourinary tract. In addition, the presence of C. trachomatis infection is associated with a risk of developing cancer of the cervix and ovaries. Features: small genome, lack of own mitochondria. The survival and replication of bacteria depends on the amino acids and nucleotides of the host cell. Chlamydia exists in a conflict situation, because it needs metabolites from a living host, but it harms the cells of the host organism and causes DNA damage.

A study by scientists at the Max Planck Institute for Infectious Biology found that C. trachomatis infections alter histone epigenetic labels, affecting the DSB kinase marker γH2AX activity. Previously, it was shown that ROS produced during chlamydial replication cause oxidation of membrane lipids, and ROS also contribute to the formation of DSB, however, C. trachomatis was found to impede the normal flow of DDR in response to DNA damage, preventing access of key ATM and 53BP1 proteins to damaged areas. Despite breaking the DDR, Chlamydia-infected cells continued to proliferate, supported by enhanced oncogenic signals involving ERK, Cyclin E and SAHF [1].

Thus, C. trachomatis infected cells host organism with damaged DNA and modified chromatin are forced to survive due to DSB restoration and cell cycle

regulation, and chlamydia creates an environment conducive to successful survival and reproduction.

9. Streptococcus pneumoniae

Streptococcus pneumoniae is a gram-positive anaerobic, one of the main causative agents of pneumonia in children and adults.

Recently, it has been studied that streptococcus bacterium is able to infect human cells and lungs, as it contains a specific pyruvate oxidase (SpxB) gene, which enhances the secretion of hydrogen peroxide, this leads to endogenous oxidative stress, followed by the induction of DSB and consequently apoptosis.

There have been other studies that have demonstrated that a key factor in S. Pneumoniae infection ability is the toxin, a cholesterol-dependent cytolysin (CDC-toxin), which forms pores in the cell membranes of the host body, and is involved in inflammatory reactions.

In 2016, the researche was done which results showed that DNA damage caused by a toxin precedes cell cycle arrest and induces apoptosis. In addition, the authors noted that at the stage of DNA replication, DSB is more common when exposed to pneumolysin. This observation increases the likelihood that DSBs may result from a replication fork failure. Together, the results of this study confirmed the previously unrecognized ability of pneumolysin to induce DNA damage, which is important for understanding the pathophysiology of infection S. pneumoniae.

10. Sulfate-reducing bacteria

The following bacteria are colonizers of the human intestinal tract. These bacteria are involved in inflammatory bowel diseases, the occurrence of colorectal cancer [1]. Hydrogen bacteria (Sulfidogenic bacteria, Fusobacterium nucleatum etc.) metabolize organic and inorganic sources of sulfur, produce hydrogen sulfide, and reduce sulfates. It is noteworthy that H2 and S, due to their direct genotoxicity, is a significant bacterial metabolite that can initiate colon cancer. Now, there is a connection between individual bacterial sulfate reductants (Fusobacterium nucleatum) and epithelial colorectal cancers.

Finally, we can say that this work allowed us to understand the following issues: bacterial genotoxins and bacterial eukaryotic DNA damage effectors. As the result of research, we examined the ability of some bacteria to damage DNA, the mechanisms that they use for this. The topic is relevant today, because the microbiota has a significant, and sometimes decisive, effect on the homeostasis of the host organism.

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ОСОБЕННОСТИ ФУНКЦИОНИРОВАНИЯ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ У СТУДЕНТОВ С РАЗЛИЧНОЙ УСПЕВАЕМОСТЬЮ

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FEATURES OF FUNCTIONING OF THE CARDIOVASCULAR SYSTEM IN STUDENTS WITH DIFFERENT ACADEMIC PERFORMANCE

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Аннотация. В статье рассмотрен анализ вариабельности сердечного ритма у студентов с учётом их успеваемости и уровня личностной тревожности (ЛТ).

Annotation. The article considers the analysis of indicators of regulatory systems activity and studies the effect of personal anxiety level on them.

Ключевые слова: личностная тревожность, вариабельность сердечного ритма, регуляторные системы организма.

Key words: personal anxiety, HRV (heart rate variability), body regulatory systems.

Введение

Работа регуляторных систем организма [4] может оцениваться некоторыми методами для получения данных об адаптационных возможностях организма в целом и использоваться в диагностических целях. Одним из таких методов является оценка вариабельности сердечного ритма (ВСР), основывающаяся на использовании данных о длительности интервалов между сердечными сокращениями и позволяющая оценить активность адаптивных систем организма. Оценка вариабельности сердечного ритма позволяет выявить