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FEATURES OF DNA REPAIR MECHANISMS IN HUMAN-INFECTING BACTERIAL PATHOGENS

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ABSTRACT

Studies on bacterial DNA repair mechanisms have historically been carried out in *Escherichia coli* as the model system. However, evidence is accumulating that DNA repair mechanisms in other bacterial species may differ fundamentally from those of *E. coli*. Pathogens such as *Mycobacterium tuberculosis, Helicobacter pylori,* and *Staphylococcus aureus* have evolved various DNA repair mechanisms that help them to persist. When bacterial pathogens enter the human body they are exposed to a range of host defense mechanisms, such as the formation of reactive oxygen species and reactive nitrogen intermediates that can induce mutations in their genomes. Bacterial infections can induce a range of pathogenic diseases, and each of the causative bacterial species has characteristic DNA repair mechanisms. The study of the functions and biological roles of DNA repair enzymes is very important for understanding bacterial persistence in the human body. Moreover, repair enzymes might be potentially new targets for therapeutic agents. In this study, the DNA repair mechanisms of various human pathogens are described.

Keywords: DNA repair, *Mycobacterium tuberculosis, Helicobacter pylori, Staphylococcus aureus.*

INTRODUCTION

DNA repair is an essential mechanism for all living organisms. Research on *E. coli* DNA repair pathways was started about 60 years ago, today *E. coli* is the most thoroughly characterized organism among all bacteria. Nevertheless, more and more evidence is accumulating that not all bacteria function as *E. coli*. In order to get a broader picture it is necessary to analyze various groups of bacteria.

A reduced number of genes of DNA repair enzymes was detected during comparing DNA repair enzymes of various bacteria in comparison with *E. coli*. For example, in the case of base excision repair often not all pathogens have *nei*, *alkA*, *nfi*, *nfo*, *tag* and *xthA* genes as in *E. coli* [1]. In some pathogens key enzymes of different repair pathways are absent. On the one hand, the lack of functions of repair pathways leads to changes in the genome. On the other hand, pathogens may have genes that code for functionally identical products, but these genes do not have a homologous sequence. In this context, it remains relevant to search for new genes and RNA which encode repair enzymes.

This article focuses on DNA repair mechanisms for human pathogens *H. pylori*, *M. tuberculosis* and *S. aureus*, as well as the role of DNA repair in the infection and persistence of these bacteria.

MYCOBACTERIUM TUBERCULOSIS

The genome of tuberculosis causative agent (*M. tuberculosis*) includes a variety of genes involved in various DNA repair mechanisms, such as base excision repair (BER), nucleotide excision repair (NER), non-homologous end joining pathway (NHEJ) etc. However, there are significant differences from the studied microorganisms: the absence of gene homologs of mismatch repair pathway, the presence of some

repair genes found exclusively in eukaryotic cells. Another distinctive feature of *M. tuberculosis* is its ability to persist latently for a long period of time. Being in a practically non-deviding state inside macrophages, mycobacteria should have effective DNA repair mechanisms to preserve genomic stability.

M. tuberculosis is a gram-positive bacterium that causes tuberculosis, a disease that is one of the most common causes of mortality of infectious nature. According to the World Health Organization (WHO), in 2015 10,4 million people became ill in the world, 480 000 patients suffered from multidrug-resistant tuberculosis and 1,4 million people died. Tuberculosis (TB) remains one of the top ten causes of death worldwide. In 2015, more than 15 000 new cases were detected in Kazakhstan. In 2015 the share of cases of multidrug-resistant tuberculosis from the number of new cases was 25%. According to WHO, Kazakhstan is one of the top five countries for the prevalence of multidrug-resistant tuberculosis. Therefore, the study of factors and fundamental foundations of the occurrence of mutations leading to antibiotic resistance is a highly topical priority task of science and public health. Treatment of TB requires long-term use of anti-tuberculosis drugs. Combating TB is one of the priorities of Kazakhstan's healthcare. TB causes huge human losses, as well as negative social and economic consequences of the country.

M. tuberculosis is a member of *Mycobacterium tuberculosis* complex, which includes various types of mycobacteria that are capable to cause TB: *Mycobacterium tuberculosis*, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium bovis BCG*, *Mycobacterium canetti*, *Mycobacterium caprae*, *Mycobacterium pinnipedii* and *Mycobacterium microti*. As an intracellular pathogen, *M. tuberculosis* should have an effective DNA repair system to support the genome integrity.

Base excision repair

Sequencing of the genome of *M. tuberculosis* has shown that it contains many genes of base excision repair pathway. The pathogen genome is 66% GC-rich. It should be expected that there is a high probability of mutations in the form of deamination of cytosine to uracil and oxidation of guanine to 8-oxoguanine (8-oxoG).

Base excision repair is a DNA repair pathway aimed to remove the damaged base. The first step of BER pathway is excision of the damaged base with an enzyme class called DNA glycosylases [2]. The DNA glycosylase catalyze the hydrolysis of the N-glycosidic linkage between chemically modified or inappropriate bases and a sugar-phosphate backbone. The initial enzymatic process of the BER pathway forms DNA regions without bases, these sites are called apurinic/apyrimidinic (AP) sites. The presence of unprocessed AP sites can be more damaging than the modified bases, since they interfere with such important cellular processes as replication and transcription. Accumulation of AP sites in DNA has a mutagenic and cytotoxic effect. AP sites can also be formed as a result of depurinization or depyrimidization due to spontaneous hydrolysis of the N-glycosidic bond. The removal of AP sites is initiated by enzymes called apurine/apyrimidine (AP) endonucleases, which specifically recognize these sites. AP endonucleases form cuts or «nicks» in DNA duplex by hydrolysis of the phosphodiester bond (the phosphodiester bond is cut off) to form the 5'-terminal deoxyribose-phosphate residue. BER pathway is completed by filling the corresponding nucleotide and ligating the DNA (fig. 1).

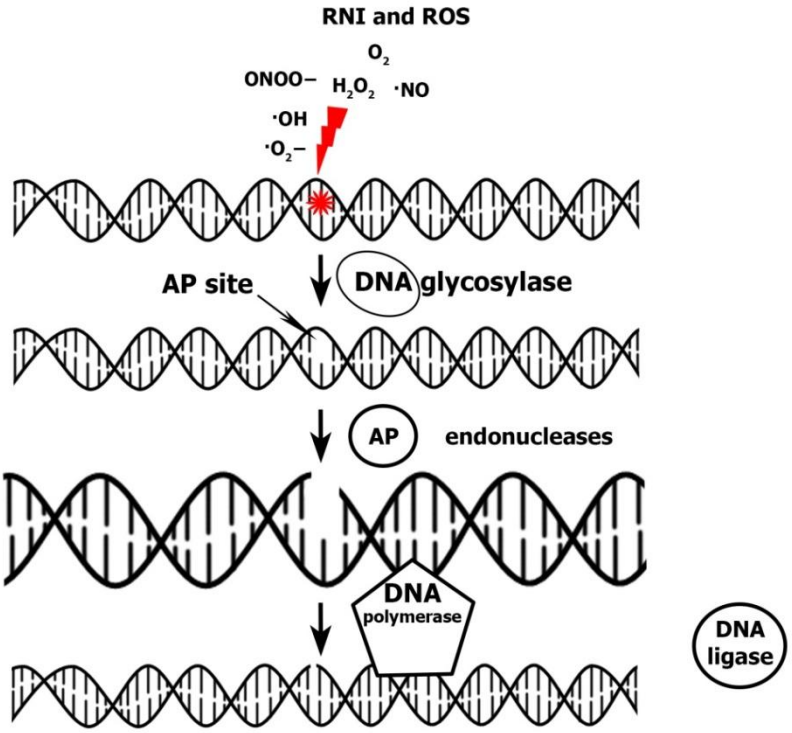

Fig. 1. Schematic representation of the base excision repair pathway

Thus, AP endonucleases are key proteins involved in BER. *xthA* and *nfo* (*end*) genes were identified in *M. tuberculosis* as Rv0427c and Rv0670, respectively. Studies have shown that these enzymes have 3'-phosphodiesterase and 3'-phosphatase repair activities in addition to AP endonuclease and 3'-exonuclease activities. The data showed that, in the absence of metal cofactors, mycobacterial AP endonucleases have very low cleavage activity of the AP site. The addition of divalent cations greatly stimulates DNA repair activity. It is known that being inside granulomas, mycobacteria are exposed to a high level of oxidative stress, nutritional starvation, hypoxia and acidic pH. Results suggest that AP endonuclease activity of mycobacterial enzymes can be tightly regulated by pH and chemical nature and concentration of divalent cations *in vivo*. These properties can help bacteria adapt to changing conditions at different stages of infection. It is likely that it can be assumed that inside the phagosome mycobacterial AP endonucleases can reach their maximum cleavage activity of AP sites [3, 4].

Nucleotide excision repair

NER pathway was the first identified pathway that repairs thymine dimers as a result of exposure to UV radiation. Studies of UV-induced mutagenesis, cell death, and sensitivity to ionizing radiation have laid the foundation for DNA repair.

NER begins when UvrA dimer (UvrA2) forms a triple complex with UvrB [(UvrA2) (UvrB)] and recognizes DNA damage in the ATP-dependent process. UvrC endonuclease takes part in cleavage of the fourth or the fifth nucleotide below from the lesion site and 7 or 8 nucleotides upward to the lesion, which results in the removal of the ~12-13-mer oligonucleotide. UvrD, DNA helicase, removes the damaged DNA together with the protein complex, «clearing» the pathway for DNA polymerase to complete repair synthesis (fig. 2, table 1).

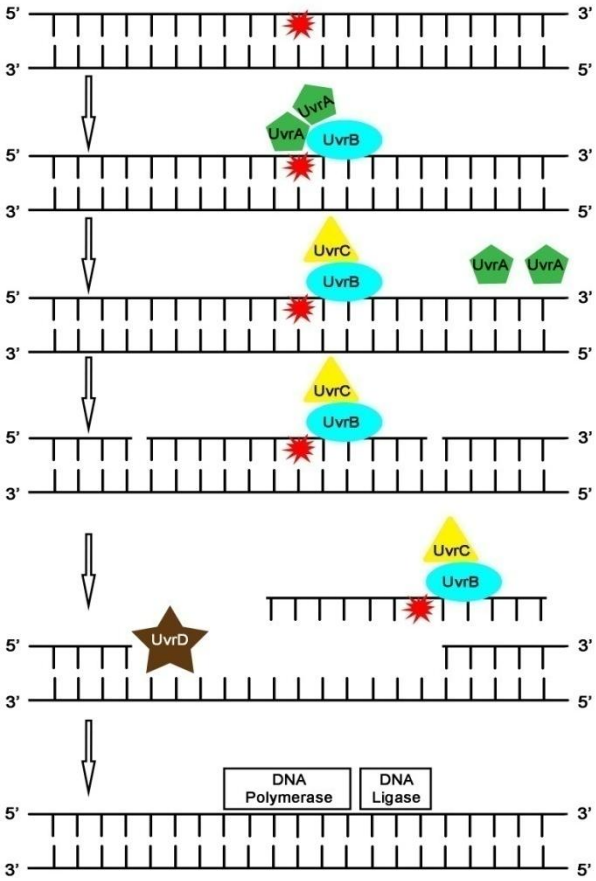

Fig. 2. Schematic representation of nucleotide excision repair pathway

Table 1. List of enzymes of *M. tuberculosis* involved in BER and NER pathways

Enzyme	Locus	Function	Reference
Ung	Rv2976c	Removal of uracils	[5]
UdgB	Rv1259	Removal of uracils	[6]
Fpg1 (MutM)	Rv2924c	Recognizes the AP site opposite G, T and C, less active opposite A. Removal of 8-oxoG opposite C (8-oxoG:C> G ~ T ≫ A)	[7]
Fpg2	Rv0944	Does not show DNA-binding activity	[7], [8]
Nei1	Rv2464c	Recognizes oxidized pyrimidines in single-stranded and double-stranded DNA. Substrates are Tg (thymine glycol), DHU (5,6-dihydrouracil), urea and AP site	[7], [8]
Nei2	Rv3297	Absence of in vitro activity. When complemented, reduces the frequency of spontaneous mutations	[7]
Nth	Rv3674c	Substrates are DHU, urea, AP site, 5-OHU (hydroxyuracil) and 5-OHC (hydroxycytosine)	[7]
MutY	Rv3589	Excision A opposite 8-oxoG	[9]
TagA	Rv1210	3-methyladenine glycosylase. Biochemical characteristic of the enzyme has not been carried out	
AlkA	Rv1317c	Methyltransferase activity	[10]

Mpg	Rv1688	Excision of hypoxanthine. A complete biochemical characteristic of the enzyme has not been carried out	[11]
XthA	Rv0427c	Processing the AP site. The presence of 3'-repair phosphodiesterase, 3'-phosphatase and 3'-exonuclease activities	[3], [4]
Nfo	Rv0670	Processing the AP site	[3], [4]
UvrA	Rv1638	Component of nucleotide excision repair. Repair of nitrosative and oxidative DNA damage	[12]
UvrB	Rv1633	ATPase activity. Structural-specific ATP-dependent DNA helicase activity	[13]
UvrC	Rv1420	*uvrC* mutant is sensitive to UV	[14]
UvrD1	Rv0949	*uvrD1* mutant leads to a small colony phenotype. The mutant strains showed increased susceptibility to representatives of the active forms of oxygen and nitrogen	[15]
UvrD2	Rv3198c	Helicase with DNA-dependent ATPase activity	[16]
XPB (ercc3)	Rv0861c	3'→5' DNA repair helicase with DNA-dependent ATPase activity	[17]

Non-homologous end joining pathway

The study of DNA repair in bacteria in the vast majority of studies relies on knowledge obtained from experiments on a model organism – *Escherichia coli*. However, in the case of the causative agent of tuberculosis, there are significant differences: both in the functions of some enzymes, in new repair enzymes that were not previously found in prokaryotic cells, and at the level of new repair pathways. For example, the mechanism of non-homologous end joining.

During replication or as a result of exposure to DNA-damaging agents, double DNA breaks occur that are lethal if they are not repaired. Double-strand DNA breaks can be repaired both by homologous recombination and by a non-homologous end joining. This repair mechanism was discovered relatively recently, and it includes Ku DNA-binding protein and LigD DNA-ligase [18]. The presence of this repair mechanism in mycobacteria appears to play an important role in disease pathogenesis.

Mismatch repair pathway

During DNA replication by polymerase, non-complementary nucleotides are mistakenly incorporated. In *E. coli*, there is a mechanism for repairing erroneously paired nucleotides - mismatch repair pathway, which is represented by the enzymes MutS, MutH and MutL. The mechanism for detecting the mismatch is carried out by MutS protein, which recognizes mispairs. Further, MutL is connected to MutS, the second component of the mismatch repair system. MutL, in turn, activates MutH, which makes an incision near the mismatch, and then UvrD unwinds DNA strand from the incision site to mismatch. The exonuclease removes the displaced strand, creating a single-stranded gap, which is then filled with DNA polymerase III. The resulting incision (nick) is subsequently processed by DNA ligase. Mismatch repair pathway is highly conserved in bacterial populations and originates from a common ancestor. Any changes in genomic DNA that lead to a mutation or loss of the mismatch repair system can lead to a higher mutation rate incidence of pathogen, which can lead to the emergence of resistant strains.

Homologues of mismatch repair have not been identified in mycobacteria. This circumstance has significant consequences in the stability of the genome. Nevertheless, the *M. tuberculosis* genome is very stable. The discovery that mycobacteria have the same mutation rate comparable to other microorganisms possessing MMR system suggests that *M. tuberculosis* has alternative or compensatory strategies for recognizing mispaired nucleotides. Experiments were performed to determine the mutation rate *in vitro*, which was $2{,}9\times10^{9}$ per base pair per round of replication, which is comparable to *E. coli*. However, *E. coli* has postreplicative mismatch repair pathway. Mutants of *E. coli* on the mismatch repair genes have an increased mutation rate. It is possible that the newly discovered mismatch-specific endonuclease is an alternative to the absence of a canonical repair system [19]. Interestingly, MutS and MutL enzymes are absent in almost all representatives of the class of actinobacteria.

HELICOBACTER PYLORI

Helicobacter pylori is one of the most common pathogens. The level of infection declined in economically developed countries in the 20th century. But even today 50% of the world population carry this pathogen. At most of colonized people *H. pylori* does not cause any symptoms. However, prolonged carrier of *H. pylori* significantly increases risk of certain diseases' developing: a peptic ulcer disease develops approximately in 10% of infected individuals, gastric adenocarcinoma – in 1-3%, and MALT-lymphoma – in <0,1% [20]. In the early stages MALT-lymphoma can be cured by destroying the first clones with antibiotics. According to statistics of WHO for 2014, Kazakhstan ranks fifth in the world in mortality terms from gastric cancer (19,41 cases per 100 000 people). Gastric cancer is detected in men twice more often than in women.

H. pylori is a gram-negative spiral bacterium having 3-5 polar flagella for movement in the gastric mucosa. The pathogen lives in the mucous membrane, as well as in close proximity to the epithelial cells of the stomach. Elimination of *H. pylori* by improving hygiene, housing, and antibiotic treatment strongly correlates with a decline in gastric cancer worldwide.

In 1994 *H. pylori* was recognized as a carcinogen of group 1. Now this pathogen is considered the most common etiologic agent of a cancer infection, accounting for 5,5% of all cancers [21]. In 2005, Barry Marshall and Robin Warren were awarded the Nobel Prize in Physiology or Medicine for the discovery of the bacterial nature of gastritis, as well as gastric and duodenal ulcers.

Proteins of DNA repair and recombination play an important role during *H. pylori* infection. After penetrating the gastric mucus the bacterium is in close proximity to stomach epithelial layer and it causes innate immune responses, followed by ROS and RNI produced by epithelial cells and phagocytes. Pathogen acquires DNA damage, which must be corrected to survive in such conditions. The pathogen has a minimal set of enzymes of BER, but it does not have functioning pathways of mismatch and non-homologous joining of the ends [22].

Furthermore, recombination provides phenotypic diversification during infection, it facilitates development of chronic infection and survival in changing environment. The genetic diversity of *H. pylori* strains is of considerable interest to researchers to study pathogenesis, because allelic variations in several genes (including CagA and VacA exotoxins) correlate with disease risk and partly explain differences in the incidence of *H. pylori*-related diseases among humans [23]. Genetic diversity makes it possible to study structure of a bacterial population. *H. pylori* strains retain the characteristic properties of the clone from which they originated. Clones occurred in parallel with the ancient migrations of his human host, which suggests a relative isolation of bacterial populations within closely related hosts. But there are data on the presence of impurities among strains in geographic regions, this fact indicates the horizontal transfer of genes and recombination between strains. The initial genome analysis suggested that *H. pylori* does not have many homologous recombination and repair genes necessary to maintain the genome integrity against polymerase errors, as well as endogenous and exogenous DNA-damaging agents [22, 24]. However, many of these pathways exist and are partially missed because *H. pylori* belongs to *Epsilonproteobacteria* evolutionary group, which is completely different from the model gram-positive pathogens *Escherichia coli* and *Salmonella.*

Many research teams have tested the ability of various mutants to colonize a mouse model of infection to begin research on the role of DNA repair and recombination during *H. pylori* infection.

Base excision repair

BER can correct damages of bases caused by oxygen radicals, which are by-products of the metabolism and effectors of the host's immune system. Guanine is particularly sensitive to reactive oxygen, the predominant product of damage is 8-oxoguanine. The pyrimidines also undergo oxidation, forming thymine glycol and 5,6-dihydrothymine. Although oxidized purines are more numerous in comparison with oxidized pyrimidines, former are mutagenic. Oxidized pyrimidines are able to inhibit DNA replication and transcription, so they are cytotoxic. Components of *H. pylori* base excision repair have a higher specificity for cytotoxic base lesions than for mutagenic. The high mutation rate promotes high genetic variability due to decreased correcting ability of DNA polymerase, which allows *H. pylori* to adapt to stress conditions of stomach. Since there is no competition of *H. pylori* with other microorganisms in aggressive gastric environment, the loss of a part of populations due to mutations does not cause serious damage. Moreover, a high mutation rate is beneficial for *H. pylori*, than for other pathogens that live in «densely populated» parts of human body.

Three DNA glycosylases were identified in *H. pylori*: endonuclease III (Nth), 3-methyladenine DNA glycosylase (Mag III), and uracil DNA glycosylase (Ung). Bifunctional DNA glycosylase Nth removes oxidized pyrimidines and AP-site. Mutant strains that do not have Nth are sensitive to oxidizing agents and they are destroyed by activated macrophages [25]. Monofunctional DNA glycosylase Mag III contains structural motifs similar to *E. coli* AlkA DNA glycosylase. Mag III is highly specific for 3-methyladenine due to structure of the binding domain, eliminating 7-methylguanine and other methylated bases: 3-methylguanine inhibits DNA synthesis, 7-methylguanine has only mutagenic properties. MagIII

is essential for survival in the case of alkylation stress and stomach colonization. All nitrogenous bases are prone to spontaneous deamination, hydrolysis of cytosine to uracil is the most often modification. In DNA uracil is recognized and eliminated by Ung-DNA glycosylase. Despite the fact that Ung-DNA glycosylase is not described in detail, it is known that it is important for stomach colonization [26].

Another feature of *H. pylori* BER pathway is presence of single AP-endonuclease and the absence of the oxidized guanine DNA repair system (GO-system). In *E. coli* MutY glycosylase cleaves the inappropriate adenine, most of these discrepancies appear when guanine is oxidized to 8-oxoguanine. Since 8-oxoguanine can be complementary to cytosine and adenine, this leads to mutations if the lesion is not corrected prior to DNA replication. Inactivation of MutY provokes a significant rate increase of cytosine transduction to adenine in *E. coli*. MutY homolog was identified in *H. pylori*, which involved in restriction of transversal mutations. MutY inactivation leads to total rate rising of point mutations in 3,7 times, and more than in 300 times at specific sites. MutY reduces the spontaneous mutation rate, it has been proven on *H. pylori* mutant strains that do not have *mutY* gene. Moreover, MutY promotes stomach colonization by *H. pylori* [27].

Thus, *H. pylori* inhabits in gastric mucosa in close proximity to epithelial cells and migrating neutrophils, exposing the pathogen to an «oxidative burst». The high specificity of BER pathway enzymes to cytotoxic DNA damages, not to mutagenic ones, causes high genetic variability and mutation rate, that is often found in *H. pylori* strains. There is a slight redundancy of DNA glycosylases at the level of DNA damage recognition.

Nucleotide excision repair

NER recognizes and restores a large number of bulky lesions. UvrABC recognizes distortions in DNA double helix, but not specific lesions. It creates a universal DNA repair system. The homologues of *uvrABCD* were observed in *H. pylori* genome, but unlike *E. coli* these genes are scattered throughout the whole genome. This indicates the existence of mechanism for coordinating regulation or constitutive expression of genes [22]. *ΔuvrD* mutants of *E.coli* and *H. pylori* are sensitive to UV irradiation, and the ultraviolet sensitivity of *E.coli* mutants can be partially restored by *uvrD* of *H. pylori*. *ΔuvrB* mutant has a high sensitivity to UV damage, methyl methanesulfonate and acid, that indicates important role of NER pathway for maintaining DNA stability in environment with a low pH of human stomach [28].

During transcription in *E. coli* RNA polymerase periodically occurs with mutated bases that block transcription. Transcription binding factor Mfd interacts with stopped polymerase. Next, it actively recruits UvrABC complex to participate in transcription-related repair. *H. pylori* has a homologue of Mfd, *mfd* mutants are more sensitive to a number of antibiotics (clarithromycin, amoxicillin and metronidizol), as well as to DNA damaging agent mitomycin C. This sensitivity points to possible additional role of Mfd in recombination [29].

Mismatch repair

H. pylori does not have mismatch repair, although MutS2 homologue is expressed. This enzyme with high affinity for double-stranded DNA containing 8-oxoG inhibits homologous recombination. In addition, MutS2 homologue protects cells from oxidative stress by an unknown mechanism.

The absence of a mismatch repair system can explain the high variability of some strains of *H. pylori*. Alternatively, *H. pylori* can preserve mismatch repair system independently from MutL. Although, there is no specific evidence of required endonuclease. It has been suggested that MutS2 can recognize an erroneous nucleotide and provide a substrate for the enzyme that performs function of MutH in *E. coli* [30]. Some *H. pylori* strains have low mutation rates, additional studies are justified for further ascertaining of alternative mismatch repair system.

Homologous recombination

Homologous recombination is an important mechanism for *H. pylori*, which enhances genetic diversity through deletions, insertions and duplication of genes. The homologous recombination pathways of *E. coli* are largely preserved in *H. pylori* with important mechanical modifications. There are separate enzymes to interact with a double-stranded DNA break and individual enzymes for single-stranded DNA breaks to activate RecA. In *E. coli* presynaptic pathways are overlapped, available data suggest that presynaptic pathways are independent in *H. pylori* [31].

Blocked replication forks can cause breakdown of double-stranded DNA during transcription and DNA synthesis. In *E. coli* RecBCD complex provokes double chain breaks and it releases the filament at the 3'-end of the single-stranded DNA for attachment of RecA. In many alpha-, betaproteobacteria and all epsilonproteobacteria, including *H. pylori*, AddAB complex performs similar activities. Both subunits of AddAB complex have a nuclease domain, AddAB has an additional ATP-dependent helicase activity. In *E. coli* RecBCD-dependent recombination can be restored almost to wild-type level due to AddAB from *H. pylori*, but only in the presence of RecA from the same pathogen. This provides convincing evidence that AddAB is necessary for the binding of RecA to the ends of single-stranded DNA; this process facilitates exchange and recombination of chains. RecBCD enzyme of *E. coli* is regulated by *chi-*

sequences, but *chi*-sequences are not common in *H. pylori* genome. The mechanism that triggers switching of AddAB from nucleolytic activity to RecA-binding activity remains unknown. It should be noted that RecA is an important protein for almost all recombination events in *H. pylori*. RecA binds to single-stranded DNA, after that it mediates the pairing of the homologous sequence, and RecA is necessary for natural competence and resistance to many DNA damaging agents [32].

H. pylori has *recO*, *recR* and *recJ*, but this pathogen does not have *recF* and *recQ*. RecOR is involved in repair of ruptures and restarting of the replication fork, presumably similar to *E. coli*. RecOR activity is dependent on RecA and probably RecOR facilitates the attachment of RecA to the ends of single-stranded DNA in a manner analogous to *E. coli*. RecOR plays an essential role in the resistance to rupture of single-stranded DNA caused by UV irradiation and the intragenomic recombination [31]. It was found that mutants not carrying *addA* and *recO* genes have the same sensitivity to factors that lead to double-strand breaks, as in mutants not carrying *addA* gene. This means that RecOR pathway does not participate in the repair of double-stranded ruptures, even in the absence of AddA. This contrasts with the partial redundancy of the two pathways in *E. coli*.

H. pylori has homologues of RecN and RecJ nucleases, but not RecQ. RecN nuclease is necessary for a high natural transformation rate and resistance to oxidative and acid stress. Different mutants that do not have 2-3 genes (combinations of *recO*, *recR*, *addA* and *addB*), show the same sensitivity to UV and ionizing radiation as *recA* mutant. It is unlikely that RecJ and RecN are involved in alternative presynaptic pathways [31]. Research should be conducted to identify how these proteins interact with AddAB and RecOR pathways, as well as with specific types of DNA damage.

H. pylori has RuvABC homologue, and *ΔruvC* mutant is sensitive to oxidative stress, similar to *E. coli*. Helicase RecG in combination with RusA nuclease or RuvABC regulate Holliday junction in *E. coli*. Although *recG* from *H. pylori* can complement the UV-induced lethality of *recG* mutant of *E.coli*, *recG* mutant of *H. pylori* is insensitive to UV radiation. Since *H. pylori* does not have RusA homologue [33], it has been suggested that *RecG* from *H. pylori* cannot regulate Holliday junction, instead it stops recombination by acting as a limiting regulator of recombination. Post-synaptic pathways are the basis of *H.pylori* DNA repair system, these pathways save basic functions with some differences from *E. coli.* As in the case of RecG, proteins may function in other way than *E. coli* or greater redundancy has been lost during genome contraction.

Thus, *H. pylori* has allelic diversity and genetic variability, that are usually caused by point mutations and recombination. This leads to infection of each person by specific strain; however, the differences between related strains are minimal. Allelic diversity is caused by significantly higher level of mutations than in many other bacteria [34], that can also explain the rapid development of resistance to commonly used antibiotics, such as clarithromycin. The high mutation rate is most likely due to the absence of mismatch DNA repair (*mutS1*, *MutL*, *mutH*) and several enzymes of base excision repair [35].

The loss of several proteins of DNA repair in *H. pylori* causes a slower colonization, that is usually observed a week later, and a decrease in persistence, that is usually observed a month later, in the mouse model. For more successful and rapid colonization of *H. pylori* the following DNA repair proteins are required: Xth endonuclease (repair of oxidized pyrimidine residues), MutS2 (recognition and cleavage of 8-oxoguanine), Nth and MagIII DNA glycosylases. In addition, all tested genes for recombinant repair are necessary for effective stomach colonization: *addAB*, *recN*, *recO*, *ruvC* and *recA*. *ΔrecA* mutant was the most non-viable phenotype in which colonization was not detected, it illustrates involvement of RecA in numerous repair pathways.

STAPHYLOCOCCUS AUREUS

Man is the natural reservoir of *S. aureus*, which provokes most infections of skin and soft tissue: impetigo, folliculitis, cellulitis and infected ulcers and wounds [36]. In addition, *S. aureus* is one of reasons of invasive and life-threatening infections: bacteremia, abscess, pneumonia, osteomyelitis, meningitis, endocarditis and sepsis. Patients with the following diseases and circumstances are particularly susceptible to infections: type 1 diabetes, intravenous medication, surgery, patients with AIDS. Patients who have quantitative and qualitative defects of leukocytes are also at high risk of developing *S. aureus* infections [37].

The ability of *S. aureus* to cause such a wide range of infections is determined by a variety of virulence factors and resistance to numerous antibiotics. *S. aureus* is the most famous causative agent of nosocomial and community-acquired infections, since it lives in the nasal cavity of 20-30% of people [38] and it is able to evade the mechanisms of protecting the immune system of the host [39].

Treatment of infections is complicated by detection of methicillin-resistant strains of *S. aureus* (MRSA), multidrug resistance antibiotics of which increases. In the US mortality statistics from invasive infections caused by MRSA are increasing yearly (~ 18,500) compared to other single infectious agents associated with HIV, viral hepatitis and influenza [40]. MRSA infections are endemic in hospitals around the world, MRSA can cause infections in healthy people and MRSA are responsible for a significant

percentage of skin and soft tissue infections in the United States (> 50%), Asian countries (~ 17%) and in Europe (<1% To 32%, depending on the country) [41].

As a rule, colonies of most strains of *S. aureus* have a yellowish-orange or golden color due to the presence of carotenoid pigments. Carotenoid pigments protect *S. aureus* from drying out and photosensitivity. Also, pigments suppress toxic singlet oxygen. Carotenoids are powerful antioxidants due to their numerous conjugated double bonds, which make them an important survival factor for detoxification of ROS. The importance of staphyloxanthine in protection against ROS is demonstrated by unpigmented *crt* mutants. These mutants normally grow but they are hypersensitive to ROS, $OONO^-$ и HOCl [42]. One of consequences of this hypersensitivity to oxidants is easier elimination of *S. aureus* strains without carotenoid biosynthesis by an innate immune response. In experimental mice with subcutaneous abscess unpigmented strains of *S. aureus* have low virulence and survival as compared with pigmented wild-type strains [43].

Antioxidant properties of carotenoids cause the resistance to influence of phagocytes, that is attributed to pigments. This effect is not observed in mice with absent NADPH-oxidase or with inhibition of oxylitic explosion. In addition to antioxidant properties, staphyloxanthin can alter the rigidity of membrane, which is important to fight with protective mechanisms of human body mediated by cationic peptides [44]. Based on the above facts, inhibition of carotenoid biosynthesis is considered as a potential therapeutic target in treatment of *S. aureus* infections.

In addition to pigments, most staphylococci have several enzymes that are used to detoxify reactive intermediate products of oxygen and nitrogen: superoxide dismutase, catalase, glutathione peroxidase, globins and peroxiredoxins. Except carotenoid pigments and antioxidant enzymes, *S. aureus* is protected by repair enzymes at the level of genomic DNA, that can also be considered targets for drugs.

Excision repair

As in many aspects of bacteriology, most of knowledge was obtained during the study of model bacterium *E. coli*. Therefore, this knowledge was used to draw conclusions of DNA repair of staphylococci. Over time, these findings are likely to be confirmed, bacause *S. aureus* has homologues of many DNA repair enzymes, in particular for BER and mismatch repair pathways: Nfo, MutM, MutY, MutT, MutS, MutL, RecJ and Nth [45].

Depending on the enzymatic properties of initiating DNA glycosylase, the activity of AP-endonuclease or DNA-deoxyribose phosphodiesterase (drPase) is required to eliminate the reaction product. AP endonuclease activity is performed by exonuclease III (ExoIII or Xth) and endonuclease IV (EndoIV or Nfo), while dRPase activity is realized by RecJ and exonuclease I (ExoI) in *E. coli* [46].

As mentioned earlier, the most common damage is 8-oxoguanine (complementary to adenine), that is a result of oxidative stress. In *E. coli* formamidopyrimidine-DNA glycosylase (Fpg) recognizes oxidized purines and open purine rings, adenine-DNA glycosylase (MutY) prevents transversal mutations by removing inappropriate adenine [47]. Moreover, oxidized guanine is removed by pyrophosphohydrolase activity of Fpg DNA glycosylase.

The 5,6-double bonds of pyrimidines are sensitive to reactions with $HO^{\cdot}$, it creates a series of oxidized products. In *E. coli* pyrimidine damage is recognized by endonuclease III (EndoIII or Nth) and endonuclease VIII (EndoVIII or Nei). Removal of non-conforming bases occurs owing to mismatch system that requires MutSL to recognize and initiate excision repair. Mismatch and GO systems are important for adaptive mutagenesis and generation of genetic diversity, which is also characteristic of *S. aureus* [48].

During NER pathway damaged DNA is detected by a complex of UvrA and UvrB. After detecting of damage UvrB binds to damaged DNA, displacing UvrA and allowing UvrC to join UvrB. It is the complex of UvrBC that cleaves the phosphodiester base to create an excision of 12 base-length. UvrD promotes the dissociation of base pairing, causing the release of nucleotide segment. Then DNA polymerase synthesizes DNA again and fragments are ligated. In addition to UvrAB, the transcription-repair factor Mfd can activate mechanisms of excision repair. It is likely that this process appears to be similar to *S. aureus*, so far as it has *uvrABC* and *mfd* genes [49].

Recombination repair

Often destruction of the chain is consequence of oxidative damage of sugar in DNA, that can be repaired through mechanisms based on recombination. In *E. coli* repair of DNA double strand breaks begins when RecBCD binds to the blunt end of a double-stranded DNA rupture, and helicase activity of RecB and RecD untwists DNA. There is redundancy at the beginning of recombination repair (RecF and SbcCD pathways) because of serious consequences of chain rupture (i.e. death). While repair of most double-stranded DNA breaks is initiated by complex of exonucleases and RecBCD helicase in *E. coli*, this pathway is absent in gram-positive bacteria with a low GC content, including staphylococci. Gram-positive bacteria initiate double strand break repair using AddAB nuclease and helicase complex (functional homologues of RecBCD) or using homologous RecF and SbcCD ways. RecA binds to single-stranded DNA after initiation of recombination repair and DNA untwisting, and then it combines with

homologous sequence. Finally, RecA triggers chain recombination. RuvAB starts branch migration after recombination, and then together with RuvC cleaves Holliday junction. Process of branch migration and cleavage can also be catalyzed by RecG protein. These additional components for repair of double-stranded ruptures have been preserved in *S. aureus* (RecA, RuvAB, RecG) [49].

SOS response

If negative impact of ROS is large and stress response systems are overloaded, the SOS reaction is activated. When *S. aureus* is exposed by hydrogen peroxide, LexA is induced, which regulates the SOS response [50]. The SOS response is a highly conserved global DNA repair system that can confront multiple DNA damaging agents (fluoroquinolones, β-lactam antibiotics).

During the SOS reaction sensor protein RecA is activated by non-specific binding to single-stranded DNA formed in the middle of recombination repair or stalled replication. Activated RecA stimulates autocatalytic cleavage of the SOS transcriptional repressor LexA at the C-terminus of dimerized domain and at the N-terminus of DNA-binding domain, leading to derepression of SOS genes. When RecA no longer meets single-stranded DNA, concentration of unsplit LexA increases, and the SOS recovery system is deactivated.

DNA repair is one of strategies of *S. aureus* to protect against the effects of oxidative explosion. *S. aureus* almost constantly faces the problem of survival in the presence of exogenous and endogenous oxidants. Nowadays DNA repair mechanisms of *S. aureus* have been little studied. It is obvious that this mechanism reduces the frequency of mutations that can be lethal as for other pathogens.

CONCLUSION

Getting and losing of genetic information are not only important factors in microevoltion of bacteria, these processes are complicated functions, related with DNA repair, recombination and horizontal gene transfer. These mechanisms help to bacteria to adapt to environmental conditions and to develop pathogenic properties. According to available data, there are significant differences between the bacteria examined in this article. Some aspects of DNA repair are not researched fully, particuallary in *S. aureus*. It is necessary to conduct experiments for statement and refutation of available hypotheses. Differences in pathogen repair pathways reflect diversity of habitats and pathogenesis features.

Obtaining of detailed information about repair mechanisms should provide a deeper understanding of fundamental process, and it gives potential opportunities for development of new therapeutic agents.

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REFERENCES

1. Seeberg E., Eide L., Bjoras M. The base excision repair pathway. *Trends Biochem Sci.,* 1995, vol. 20, no. 1, pp. 391-397.

2. Lindahl T. New class of enzymes acting on damaged DNA. *Nature,* 1976, vol. 259, no. 5538, pp. 64-66.

3. Abeldenov S., Talhaoui I., Zharkov D. O., Ishchenko A.A., Ramanculov E., Saparbaev M., Khassenov B. Characterization of DNA substrate specificities of apurinic/apyrimidinic endonucleases from Mycobacterium tuberculosis. *DNA Repair (Amst),* 2015, vol. 33, pp. 1-16.

4. Puri R.V., Singh N., Gupta R.K., Tyagi A.K. Endonuclease IV Is the major apurinic/apyrimidinic endonuclease in Mycobacterium tuberculosis and is important for protection against oxidative damage. *PLoS One*, 2013, vol. 8, no. 8, pp. e71535.

5. Arif S.M., Geethanandan K., Mishra P., Surolia A., Varshney U., Vijayan M. Structural plasticity in Mycobacterium tuberculosis uracil-DNA glycosylase (MtUng) and its functional implications. *Acta Crystallogr D Biol Crystallogr*, 2015, vol. 71, Pt. 7, pp. 1514-1527.

6. Srinath T., Bharti S.K., Varshney U. Substrate specificities and functional characterization of a thermo-tolerant uracil DNA glycosylase (UdgB) from Mycobacterium tuberculosis. *DNA Repair (Amst),* 2007, vol. 6, no. 10, pp. 1517-1528.

7. Guo Y., Bandaru V., Jaruga P., Zhao X., Burrows C.J., Iwai S., Dizdaroglu M., Bond J.P., Wallace S.S. The oxidative DNA glycosylases of Mycobacterium tuberculosis exhibit different substrate preferences from their Escherichia coli counterparts. *DNA Repair (Amst)*, 2010, vol. 9, no. 2, pp. 177-190.

8. Sidorenko V.S., Rot M.A., Filipenko M.L., Nevinsky G.A., Zharkov D.O. Novel DNA glycosylases from Mycobacterium tuberculosis. *Biochemistry (Mosc)*, 2008, vol. 73, no. 4, pp. 442-450.

9. Kurthkoti K., Srinath T., Kumar P., Malshetty V.S., Sang P.B., Jain R., Manjunath R., Varshney U. A distinct physiological role of MutY in mutation prevention in mycobacteria. *Microbiology*, 2010, vol. 156, Pt 1, pp. 88-93.

10. Yang M., Aamodt R.M., Dalhus B., Balasingham S., Helle I., Andersen P., Tonjum T., Alseth I., Rognes T., Bjoras M. The ada operon of Mycobacterium tuberculosis encodes two DNA methyltransferases for inducible repair of DNA alkylation damage. *DNA Repair (Amst)*, 2011, vol. 10, no. 6, pp. 595-602.

11. Yang Q., Huang F., Hu L., He Z.G. Physical and functional interactions between 3-methyladenine DNA glycosylase and topoisomerase I in mycobacteria. *Biochemistry (Mosc)*, 2012, vol. 77, no. 4, pp. 378-387.

12. Rossi F., Khanduja J.S., Bortoluzzi A., Houghton J., Sander P., Guthlein C., Davis E.O., Springer B., Bottger E.C., Relini A., Penco A., Muniyappa K., Rizzi M. The biological and structural characterization of Mycobacterium tuberculosis UvrA provides novel insights into its mechanism of action. *Nucleic Acids Res.*, 2011, vol. 39, no. 16, pp. 7316-7328.

13. Thakur M., Kumar M.B., Muniyappa K. Mycobacterium tuberculosis UvrB Is a Robust DNA-Stimulated ATPase That Also Possesses Structure-Specific ATP-Dependent DNA Helicase Activity. *Biochemistry*, 2016, vol. 55, no. 41, pp. 5865-5883.

14. Parulekar R.S., Barage S.H., Jalkute C.B., Dhanavade M.J., Fandilolu P.M., Sonawane K.D. Homology modeling, molecular docking and DNA binding studies of nucleotide excision repair UvrC protein from M. tuberculosis. *Protein J.*, 2013, vol. 32, no. 6, pp. 467-476.

15. Houghton J., Townsend C., Williams A. R., Rodgers A., Rand L., Walker K.B., Bottger E.C., Springer B., Davis E.O. Important role for Mycobacterium tuberculosis UvrD1 in pathogenesis and persistence apart from its function in nucleotide excision repair. *J Bacteriol.*, 2012, vol. 194, no. 11, pp. 2916-2923.

16. Kazarian K., Cassani C., Rizzi M. Expression, purification and characterization of UvrD2 helicase from Mycobacterium tuberculosis. *Protein Expr Purif.*, 2010, vol. 69, no. 2, pp. 215-218.

17. Balasingham S.V., Zegeye E.D., Homberset H., Rossi M.L., Laerdahl J.K., Bohr V.A., Tonjum T. Enzymatic activities and DNA substrate specificity of Mycobacterium tuberculosis DNA helicase XPB. *PLoS One*, 2012, vol. 7, no. 5, pp. e36960.

18. Gong C., Bongiorno P., Martins A., Stephanou N.C., Zhu H., Shuman S., Glickman M.S. Mechanism of nonhomologous end-joining in mycobacteria: a low-fidelity repair system driven by Ku, ligase D and ligase C. *Nat Struct Mol Biol.*, 2005, vol. 12, no. 4, pp. 304-312.

19. Castaneda-Garcia A., Prieto A.I., Rodriguez-Beltran J. et al. A non-canonical mismatch repair pathway in prokaryotes. *Nat Commun.*, 2017, vol. 8, pp. 14246.

20. Peek R.M., Jr., Crabtree J.E. Helicobacter infection and gastric neoplasia. *J Pathol.*, 2006, vol. 208, no. 2, pp. 233-248.

21. Parkin D.M., Bray F., Ferlay J., Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.*, 2005, vol. 55, no. 2, pp. 74-108.

22. Tomb J.F., White O., Kerlavage A.R., Clayton R.A. et al. The complete genome sequence of the gastric pathogen Helicobacter pylori. *Nature*, 1997, vol. 388, no. 6642, pp. 539-547.

23. Wroblewski L.E., Peek R.M., Jr., Wilson K.T. Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clin Microbiol Rev.*, 2010, vol. 23, no. 4, pp. 713-739.

24. Wang G., Alamuri P., Humayun M.Z., Taylor D.E., Maier R.J. The Helicobacter pylori MutS protein confers protection from oxidative DNA damage. *Mol Microbiol.*, 2005, vol. 58, no. 1, pp. 166-176.

25. O'Rourke E.J., Chevalier C., Pinto A.V., Thiberge J.M., Ielpi L., Labigne A., Radicella J.P. Pathogen DNA as target for host-generated oxidative stress: role for repair of bacterial DNA damage in Helicobacter pylori colonization. *Proc Natl Acad Sci USA*, 2003, vol. 100, no. 5, pp. 2789-2794.

26. Baldwin D.N., Shepherd B., Kraemer P., Hall M.K., Sycuro L.K., Pinto-Santini D.M., Salama N.R. Identification of Helicobacter pylori genes that contribute to stomach colonization. *Infect Immun.*, 2007, vol. 75, no. 2, pp. 1005-1016.

27. Huang S., Kang J., Blaser M.J. Antimutator role of the DNA glycosylase mutY gene in Helicobacter pylori. *J Bacteriol.*, 2006, vol. 188, no. 17, pp. 6224-6234.

28. Thompson S.A., Latch R.L., Blaser J.M. Molecular characterization of the Helicobacter pylori uvr B gene. *Gene.*, 1998, vol. 209, no. 1-2, pp. 113-122.

29. Lee G.H., Jeong J.Y., Chung J.W. et al. The Helicobacter pylori Mfd protein is important for antibiotic resistance and DNA repair. Diagn Microbiol Infect Dis. 2009, vol. 65, no. 4, pp. 454-456.

30. Pinto A.V., Mathieu A., Marsin S., Veaute X., Ielpi L., Labigne A., Radicella J.P. Suppression of homologous and homeologous recombination by the bacterial MutS2 protein. *Mol Cell.*, 2005, vol. 17, no. 1, pp. 113-120.

31. Marsin S., Lopes A., Mathieu A., Dizet E., Orillard E., Guerois R., Radicella J.P. Genetic dissection of Helicobacter pylori AddAB role in homologous recombination. *FEMS Microbiol Lett.*, 2010, vol. 311, no. 1, pp. 44-50.

32. Amundsen S.K., Fero J., Hansen L.M., Cromie G.A., Solnick J.V., Smith G.R., Salama N.R. Helicobacter pylori AddAB helicase-nuclease and RecA promote recombination-related DNA repair and survival during stomach colonization. *Mol Microbiol.*, 2008, vol. 69, no. 4, pp. 994-1007.

33. Kang J., Tavakoli D., Tschumi A., Aras R.A., Blaser M.J. Effect of host species on recG phenotypes in Helicobacter pylori and Escherichia coli. *J Bacteriol.*, 2004, vol. 186, no. 22, pp. 7704-7713.

34. Bjorkholm B., Sjolund M., Falk P.G., Berg O.G., Engstrand L., Andersson D.I. Mutation frequency and biological cost of antibiotic resistance in Helicobacter pylori. *Proc Natl Acad Sci USA*, 2001, vol. 98, no. 25, pp. 14607-14612.

35. Suerbaum S., Josenhans C. Helicobacter pylori evolution and phenotypic diversification in a changing host. *Nat Rev Microbiol.*, 2007, vol. 5, no. 6, pp. 441-452.

36. McCaig L.F., McDonald L.C., Mandal S., Jernigan D.B. Staphylococcus aureus-associated skin and soft tissue infections in ambulatory care. *Emerg Infect Dis.*, 2006, vol. 12, no. 11, pp. 1715-1723.

37. Lowy F.D. Staphylococcus aureus infections. *N Engl J Med.*, 1998, vol. 339, no. 8, pp. 520-532.

38. Wertheim H.F., Melles D.C., Vos M.C., van Leeuwen W. et al. The role of nasal carriage in Staphylococcus aureus infections. *Lancet Infect Dis.*, 2005, vol. 5, no. 12, pp. 751-762.

39. Foster T.J. Colonization and infection of the human host by staphylococci: adhesion, survival and immune evasion. *Vet Dermatol.*, 2009, vol. 20, no. 5-6, pp. 456-470.

40. Boucher H.W., Corey G.R. Epidemiology of methicillin-resistant Staphylococcus aureus. *Clin Infect Dis*., 2008, vol. 46, Suppl 5, pp. S344-349.

41. Moran G.J., Krishnadasan A., Gorwitz R.J., Fosheim G.E., McDougal L.K., Carey R.B., Talan D.A. Methicillin-resistant S. aureus infections among patients in the emergency department. *N Engl J Med.*, 2006, vol. 355, no. 7, pp. 666-674.

42. Liu G.Y., Essex A., Buchanan J.T., Datta V., Hoffman H.M., Bastian J.F., Fierer J., Nizet V. Staphylococcus aureus golden pigment impairs neutrophil killing and promotes virulence through its antioxidant activity. *J Exp Med.*, 2005, vol. 202, no. 2, pp. 209-215.

43. Liu C.I., Liu G.Y., Song Y., Yin F., Hensler M.E., Jeng W.Y., Nizet V., Wang A.H., Oldfield E. A cholesterol biosynthesis inhibitor blocks Staphylococcus aureus virulence. *Science*, 2008, vol. 319, no. 5868, pp. 1391-1394.

44. Mishra N.N., Liu G.Y., Yeaman M.R., Nast C.C., Proctor R.A., McKinnell J., Bayer A.S. Carotenoid-related alteration of cell membrane fluidity impacts Staphylococcus aureus susceptibility to host defense peptides. *Antimicrob Agents Chemother.*, 2011, vol. 55, no. 2, pp. 526-531.

45. Ambur O.H., Davidsen T., Frye S.A., Balasingham S.V., Lagesen K., Rognes T., Tønjum T. Genome dynamics in major bacterial pathogens. *FEMS Microbiology Reviews.*, 2009, vol. 33, no. 3, pp. 453-470.

46. Mol C.D., Hosfield D.J., Tainer J.A. Abasic site recognition by two apurinic/apyrimidinic endonuclease families in DNA base excision repair: the 3' ends justify the means. *Mutat Res.*, 2000, vol. 460, no. 3-4, pp. 211-229.

47. Michaels M.L., Miller J.H. The GO system protects organisms from the mutagenic effect of the spontaneous lesion 8-hydroxyguanine (7,8-dihydro-8-oxoguanine). *J Bacteriol.*, 1992, vol. 174, no. 20, pp. 6321-6325.

48. Prunier A.L., Leclercq R. Role of mutS and mutL genes in hypermutability and recombination in Staphylococcus aureus. *J Bacteriol.*, 2005, vol. 187, no. 10, pp. 3455-3464.

49. Ambur O.H., Davidsen T., Frye S.A., Balasingham S.V., Lagesen K., Rognes T., Tonjum T. Genome dynamics in major bacterial pathogens. *FEMS Microbiol Rev.*, 2009, vol. 33, no. 3, pp. 453-470.

50. Wolf C., Hochgrafe F., Kusch H., Albrecht D., Hecker M., Engelmann S. Proteomic analysis of antioxidant strategies of Staphylococcus aureus: diverse responses to different oxidants. *Proteomics*, 2008, vol. 8, no. 15, pp. 3139-3153.

АДАМҒА ЖҰҚПАЛЫ БАКТЕРИЯЛЫҚ ПАТОГЕНДЕРДІҢ ДНҚ РЕПАРАЦИЯСЫ МЕХАНИЗМДЕРІНІҢ ЕРЕКШЕЛІКТЕРІ

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ТҮЙІН

ДНҚ репарация механизмдері негізінен модельдік жүйе ретінде *E. coli*-де зерттелген. Алайда, әртүрлі бактериялардың ДНҚ репарация механизмдері *E. coli*-ден функционалды түрде ерекшеленетінінің дәлелдері көбейіп келе жатыр. *Mycobacterium tuberculosis, Helicobacter pylori* және *Staphylococcus aureus* сияқты патогендер адам ағзасына енгеннен кейін ДНҚ репарацияның түрлі механизмдерін дамытты. Енген патогендер ағзадағы әртүрлі қорғаныс механизмдеріне тап болып, оның ішінде оттегінің реактивті түрлері (ОРТ) мен азоттың реактивті түрлерінің (АРТ) әсеріне ұшырап, патогендердің геномында мутациялардың пайда болуына әкеледі. Патогендер ДНҚ-ң жасуша ішіндегі және жасуша сыртындағы реактивті радикалдармен әсерлесуі. Жоғарыда айтылған микроағзалар туғызатын патогенезді ескергенде, әрқайсысының өзінің ДНҚ репарация механизмінің ерекшеліктері бар. ДНҚ репарация ферменттерінің биологиялық және функционалды рөлін зерттеу адам ағзасында бактериялардың өміршеңдігін түсінуге маңызды, бұған қоса репарация ферменттері антибиотиктер үшін жаңа нысан бола алады. Берілген мақалада *M. tuberculosis, H. pylori* және *S. aureus* ДНҚ репарацияның түрлі механизмдері сипатталған.

Негізгі сөздер: ДНҚ репарация, *Mycobacterium tuberculosis, Helicobacter pylori, Staphylococcus aureus*.