MOLECULAR MECHANISMS OF HELICOBACTER PYLORI ANTIBIOTIC RESISTANCE

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ABSTRACT — Currently antibiotic resistance to Helicobacter pylori (H. pylori) is considered as the main factor, defining the effectiveness of various therapy schemes for eradication of the infection. The article describes an overview of the molecular mechanisms of H. pylori resistance to the antibiotics, used in the treatment schemes of the infection.

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Nowadays the growth of *Helicobacter pylori* (*H. pylori*) strains, resistant to the main medications that are used in the schemes of the first-line therapy, is regarded as the chief reason for failure of the infection treatment. In the world population prevalence rates for *H. pylori* resistant strains vary within wide range in different geographical areas, correlating with the total worldwide frequency of antibiotics application [1]. The mechanisms of the development of *H. pylori* resistance to antimicrobials are mainly based on the point mutations, causing the change of the mechanisms of antibiotic action. The spectrum of mutations are extremely heterogeneous, as determined by different application points (targets) of antibiotics, used in eradication therapy schemes of the infection [2].

Studies of *H. pylori* resistance mechanisms to clarithromycin revealed the presence of the point mutations in the chromosomal region, encoding peptidyl transferase (the main target of macrolides) in V domain of 23S rRNA [3]. The most common variations of such mutations are the replacement of the nucleotide sequences at the positions 2142 (A2142G and A2142C), 2143 (A2143G) [3, 4]. The replacement of nucleotides in these sequences leads to reducing the affinity of macrolides to the ribosomes of the bacterial cell, thereby developing a resistance. Today other point mutations have been also described: A2115G, G2141A, T2117C, T2182C, T2289C, G224A, C2245T, C2611A, though their clinical significance in the context of antibiotic resistance has not ascertained yet, except for T2182C and C2611A, associated with low-level resistance to clarithromycin [3, 5, 6].

In addition to mentioned above changes the expression of efflux pumps of RND-family may play the role in the development of clarithromycin resistance [2, 7]. Efflux pumps are protein complexes that provide a rapid translocation (release) of medication from the bacterial cell outside, thus preventing contact of antibiotic with the ribosome [8]. The possible interaction of proton pump inhibitors (PPIs) with efflux pumps of the RND-family due to their structural analogy is of certain interest. Particularly, in addition to suppression of acid output PPIs may have an inhibitory effect on efflux pumps, reducing resistive potential of *H. pylori* [3, 9]. However, this point still does not have a substantial evidence.

Mechanisms of *H. pylori* resistance to nitroimidazole derivatives (metronidazole, tinidazole) are poorly studied. It is considered that the main reason for this resistance to the group of medications is the impossibility of antibacterial compound to transform to the active form [2]. The reasons for this phenomenon may be mutations of the RdxA gene, encoding oxygen-insensitive nitroreductase, and the FrxA gene, encoding flavin oxidoreductase [10]. Inactivation of these genes leads to the reduction in transformation (recovery) of metronidazole into the active derivatives (NO^{2-} and NO_2^{2-}), that have a damaging effect on the structure of DNA (fig. 1) [3]. Nevertheless, cases of H. pylori resistance to the nitroimidazole derivatives, not associated with mutations in the RdxA and FrxA genes have been described [11]. It is assumed that some of them may be result from low activity of the NADH-oxidase and efflux mechanisms [2, 12].
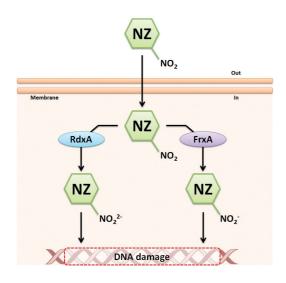
Fig. 1. *Mode of action of nitroimidazole (NZ) derivatives (metronidazole, tinidazole)*

The main reason of *H. pylori* resistance to amoxicillin is the mutation in the resistant pbp1A gene, encoding penicillin binding protein 1A (PBP1), responsible for catalyzing the terminal stage of peptidoglycan development of the bacterial cell wall [3, 13, 14]. Three variations of replacement of amino acids (Ser414 to Arg, Thr556 to Ser, and Asn562 to Tyr) in the structure of protein are the most frequently associated with amoxicillin resistance. Point mutations of the genes, encoding others of penicillin-binding proteins (PBP2, PBP3 and PBP4) are described as well. However, their role in the development of amoxicillin resistance is considered as additive [3, 14, 15].

Apart from it, the mechanisms referred to reducing the permeability of the microorganism may play a certain role in the development of H. pylori resistance to amoxicillin. The last biological characteristic is associated with the alteration of protein functions of *H. pylori* outer membrane, that are encoded by genes hopB and hopC [16].

The main reason for H. pylori resistance to tetracyclines consists in mutations in the genes, encoding 16S rRNA (*rrnA* and *rrnB*) [13, 17]. The most frequent mutation is considered to be substitution of the nucleotide triplet $AGA_{926-928} \rightarrow TTC$, that leads to reducing antibiotic affinity to the ribosome by 24–52% [3, 18]. Other mechanisms of resistance to tetracycline include activity of the protein Tet(O), which is an antagonist of the antibiotic, preventing its interaction to the ribosome and subsequent stop of the protein synthesis [19].

Fluoroquinolone (levofloxacin) resistance is associated with changes in nucleotide sequences in the gyrA gene (in positions 87, 88, 91) encoding the A subunit of bacterial DNA gyrase [2, 20, 21]. The value of the gyrB gene mutations in the development of resistance to fluoroquinolones is minimal [22].

Mechanisms of resistance to rifabutin and nitrofurans (furazolidone) are poorly studied. It is assumed that the mechanism of rifabutin resistance is associated with point mutations in the rpoB gene, encoding β-subunit of the bacterial RNA polymerase [3, 23]. Conversely the nitrofurans resistance may be mediated by mutations in the porD and oorD genes, encoding δ-subunits of the pyruvate flavodoxin oxidoreductase and 2-oxoglutarate reductase respectively [24].

Thus, in the basis of antibiotic resistance to *H. pylori* lies single point mutations and efflux mechanisms, causing an alteration of the antibacterial medication effect. The introduction of molecular genetic methods for identification of the described above mutations into clinical practice will allow for more individually approach to the treatment of *H. pylori* infection.

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