UDC 579.61:615.281.9

PATHOGENICITY FACTORS AND ANTIBIOTIC RESISTANCE OF THE *BACTEROIDES FRAGILIS*

Kozhakhmetova S.S., Zholdybayeva E.V., Mukhtarova K.E., Ramankulov Ye.M.

National Center for Biotechnology
13/5, Kurgalzhyn road, Nur-Sultan, 010000, Kazakhstan
sskozhakhmetova@gmail.com

ABSTRACT

This article presents novel ideas about classification, genomic structure (inverted regions, mobile genetic elements, plasmids, mobilized and conjugated transposons), pathogenicity factors (adhesins, various enzymes, toxins, in particular, data on enterotoxin fragmentinis BFT - *B. fragilis* toxin), and the role of their metabolites in the manifestation of pathogenicity. Data on the global prevalence of antibiotic resistance in the clinical *B. fragilis* strains are presented. Mechanisms of development of the drug resistance are considered and the role of *cfiA, tet, nim* genes in the development of antibiotic resistance is disclosed. Information on the use of the MALDI-TOF MS (matrix-activated laser desorption-ionization time-of-flight mass spectrometry) method for distinguishing *B.fragilis* strains into two groups based on the ability to carry carbapenem resistant gene (carrying and not carrying *cfiA* gene) are presented. Basics of modes of emergence of multi-resistance in clinical strains of *B. fragilis* are considered. In addition, prospects for genome-wide sequencing in predicting antimicrobial resistance are presented. Currently increasing attention of researchers is payed to increase in resistance of *B. fragilis* to widely used antimicrobials. This is indeed of a great importance when choosing adequate antimicrobial therapy.

Keywords: *Bacteroides fragilis*, pathogenicity factors, antibiotic resistance, antimicrobial therapy, the mechanisms of development drug resistance, antibiotic resistance genes.

INTRODUCTION

Bacteroides spp. are anaerobic gram-negative bacilli that colonize oral cavity, upper respiratory tract, gastrointestinal and female genital tracts [1].

Recent studies have shown that by colonizing intestines these bacteria participate in the metabolism of complex polysaccharides, modulate the local immune response, and inhibit colonization of intestines with pathogenic microorganisms. Bacteroids can be transmitted from mother to child during childbirth and, thus, become part of the human flora in the early stages of life [2]. Pathology caused by bacteroids develops most often as an endogenous infection as a result of the damage of mucous membranes, which are habitats of this microbe. Since bacteroids belong to opportunistic microorganisms, they are usually involved in polymicrobial aerobic-anaerobic infections, although they can also cause mono-infections [3]. Among all anaerobic bacteria, the *B. fragilis* are often extracted from clinical samples of patients with intra-abdominal infections, abscesses, pelvic infections, postoperative wound infections, and soft tissue infections [1].

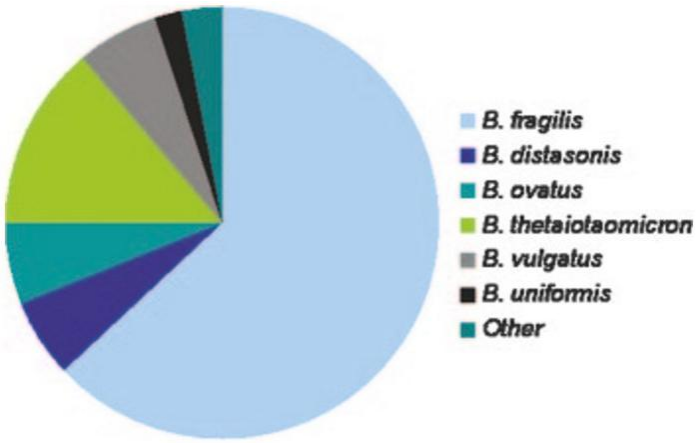

Fig.1. Distribution of the bacteroids species in a clinical isolate.

B. fragilis account for less than 0.5% of the intestinal flora, but more often than other types of *Bacteroides spp.*, are isolated from clinical specimens (Figure 1) and are the most virulent species [4].

Classification of bacteroids. The first description of bacteroids belongs to A.Veillon and Zuber who in 1898 isolated *Bacteroides fragilis* from pus in appendicitis. Subsequently, works that described anaerobic gram-negative bacilli by use of a microscopy and extraction from various inflammatory processes, as well as from the intestinal microflora of healthy people also appeared.

Accumulation of information about anaerobic non-spore-forming microorganisms, caused a need for their classification. The generic name *Bacteroides* was introduced in 1919 by Castellani and Chalmers for anaerobic rods that do not form endospores and grow on pigment-free media. Initially, this genus included both gram-positive and gram-negative rods [3].

Currently, bacteroids belong to the kingdom of bacteria, *Bacteroidetes* type, *Bacteroidia* class, *Bacteroidales* order, family of *Bacteroidaceae*, and *Bacteroides* genus. The genus contains more than 10 species (*B. acidifaciens, B. biacutis, B. distasonis, B. gracilis, B. fragilis, B. oris, B. ovatus, B. putredinis, B. pyogenes, B. stercoris, B. suis, B. tectus, B. thetaiotaomicron, B. vulgatus*). The species of *B. fragilis, B. thetaiotaomicron,* and *B. vulgatus* are of the greatest clinical importance, since, while being part of a normal microflora of the gastrointestinal tract, they most often prevail in case of intraperitoneal infections, abscesses, and pressure sores [3,5].

Genomic structure of bacterioids. The first nucleotide sequences of *Bacteroides spp.* were published in 2003-2005. A typical strain of the *B. fragilis* species NCTC 9343 has a length of 5 205 140 bp and has a GC content of 43.19%; the strain has one plasmid with 48 genes [6]. Information on the genome of *Bacteroides fragilis* YCH46 was published in 2004 (Figure 2). Its length is shown to be 5,277,274 bp, GC ratio of 43.3%; the strain has a circular plasmid pBFY46 with size of 33 716 bp [7].

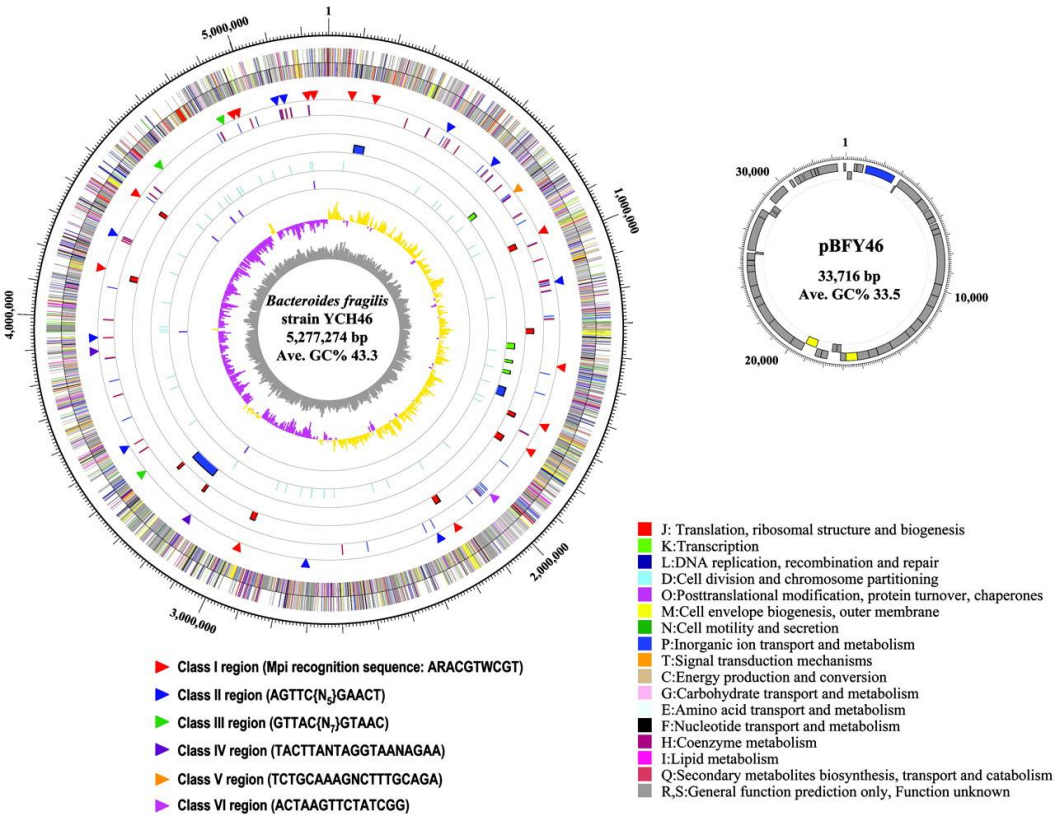

Fig.2. Genetic maps of the chromosome and the pBFY46 plasmid of *B.fragilis* strain YCH46 [7]

These studies have greatly expanded understanding of the adaptive properties and organizational structure of the bacteria. Subsequent proteomic analysis revealed the ability of this bacterium to organize environment for its own needs by interacting with a human immune system. Also, several systems for elimination of toxic substances and adaptation of metabolism to changes in nutrient substrates have been discovered in the bacteria [4].

Inverted regions in the *B. fragilis* genome. *B.fragilis* NCTC 9343 has numerous inverted regions (IRs): 16 inverted (*fin*) promoter regions that exist in addition to regions that control the PS locus (capsule polysaccharide biosynthesis) and 4 inverted DNA complexes called “shufflons”. The latter control the restriction / modification of the system, as well as the signal transduction system and two hydrocarbon recovery systems. In *B. fragilis* NCTC 9343, one of the shufflons contains insertions of conjugative transposons. It has been established that different types of shufflons usually contain different types of genes.

Some shufflons contain a large number of inverted repeats. Such inversions lead to the appearance of alternative genes encoding for an outer membrane proteins. Other types of shufflons are the fusion of silent alternative genes with a fixed promoter and the start of translation [8].

Thus, *B. fragilis* utilizes DNA inversions to control a large number of systems (including surface proteins, polysaccharides, and regulatory systems). It is assumed that hyper adaptivity provided by these systems and diversity that they give to surface structures in utilization of carbohydrates can serve as features that controll ability to colonize new sites and to avoid an immune response.

Mobile genetic elements of bacteroids. Bacteroids, just like other bacteria, have many mechanisms for exchange of genetic information. These elements play an essential role in spreading of antibiotic resistance genes. Mobile elements of *Bacteroides spp*. involved in the transmission of antimicrobial resistance genes are represented by plasmids, transposons and conjugative transposons [9]. Plasmids and conjugative transposons are the platform on which antibiotic resistance genes are assembled and sorted through various recombination systems of a bacterial cell [10].

Never the less, currently these elements are combined into a general category of integrative and conjugating elements (ICE). The ICEberg database (http://db-mml.sjtu.edu.cn/ICEberg/index.php) [11] includes 16 mobile elements for *Bacteroides spp.* species, assigning an ICE number to each.

Plasmids. Plasmids are widespread in *Bacteroides* species, and are found in 20–50% of strains [8]. Plasmids are typically replicated as separate elements inside the host cell.

Genes that confer resistance to various classes of antibiotics have been discovered in plasmids of *Bacteroides spp.* Thus, genes conferring resistance to metronidazole *nimA - F* were also found in plasmids [12]. *Bacteroides* plP419 and plP421 plasmids contain *nimC* (492 bp) and *nimD* genes (495 bp), which cause resistance to 5-nitroimidazole [13].

The *cfiA* gene responsible for resistance to carbapenem was found in a clinical isolate in pBFUK1 plasmid, with 6.4 kb mass [14].

It has been established that resistance to clindamycin and erythromycin can be transmitted between species of *Bacteroides spp*. It can be done either through a chromosome element or in association with a conjugative plasmid [15]. During a study of the prevalence of *cfiA* and *nim* genes in *Bacteroides spp*. isolates circulating in Europe, it was found that 40.0% of the isolates were *cfiA* positive and 85.7% of the isolates were resistant to imipenem. High resistance to imipenem was associated with the presence of an insertion element (IS). 21 of 640 tested strains of *Bacteroides* spp., had low susceptibility to metronidazole and only 3 strains had *nim* genes. Of these, two strains had the chromosomal localization of the *nim* gene, and one had the *nim* gene located in the plasmid [8].

Determinition and identification of plasmids in clinical isolates can help to control the spread of antimicrobial resistance.

Transposons. Mobilized and conjugated transposons are often located in the bacterial genome and are copied together with chromosomal DNA [9].

Mobilized transposons are always smaller than conjugating transposons and carry genes whose products are necessary for DNA removal and processing. Currently, the following mobilized transposons have been characterized in *B. fragilis*: 9.6KB Tn4399, 4.69KB Tn5520, 15.3KB cLV25.

Conjugative transposons (CTn) are commonly found in *Bacteroides spp*. Over 80% of *Bacteroides spp*. strains contain at least one conjugative transposon [8]. Conjugative transposons in bacteroids are often referred to as “tetracycline resistance factors,” and many of them can be stimulated by transfer through exposure to tetracycline [9]. For example, *B. fragilis* YCH46 has three conjugative transposons (CTnYCH46-1, CTnYCH46-2 and CTnYCH46-3), but only one of them CTnYCH46-1 carries the *tetQ* gene [7].

Conjugative transposons vary in size from 52 to 150 KB. For example, *B. fragilis* BTF-37 (37 KB), *B. fragilis* CTn86 (57 KB). Many conjugative transposons of B. fragilis also carry erythromycin resistance genes, such as *ermF* (cTnDOT), *ermB* (cTnBST), or *ermG* (cTnGERM1) [9].

Thus, in clinical isolates of *Bacteroides spp*. conjugative transposons are mainly responsible for the spread of tetracycline and erythromycin resistance.

Pathogenicity factors of *B. fragilis.* *B. fragilis* has a number of pathogenicity factors and, as mentioned above, is extracted in 30-60% of cases of purulent-septic nature infections, multiple organ and nonorgan abscesses in the abdominal cavity, salpingitis, endometritis, urological infection, etc. as a result of disturbance of the intestinal integrity barrier and bacterial translocation during surgical intervention and worsening of an immunity. It currently has the greatest clinical significance because of these factors.

Bacteroid pathogenicity factors are associated with resistance to the human immune system, adhesion and tissue destruction. Currently, following factors are distinguished [3]:

1. Adhesins: lectin-like surface proteins; pili; capsule.
2. Enzymes: superoxide dismutase; neuraminidase; hyaluronidase; fibrinolysin; collagenase; deoxyribonuclease; heparinase; IgA protease; β-lactamase.
3. Toxins: endotoxin; enterotoxin; leukocidin.
4. Metabolites.

The surface structures of the cell (lectin-like surface proteins, pili and capsule) provide adhesion to the substrate and protect microorganisms from phagocytosis.

The most well-studied pathogenicity factor of *B. fragilis* is a polysaccharide capsule. It is known that it includes up to eight different polysaccharides: PSA, PSB, PSC24, PSD, PSE, PSF, PSG and PSH, allowing it to modulate surface antigenicity and evade the immune response of a macroorganism [16]. Among *B. fragilis* polysaccharides, the greatest contribution to the development of peritonitis and sepsis is made by the PS-A polysaccharide [17].

It is well known that one of the negative factors for *B. fragilis* (as an anaerobic microorganism) is oxygen. However, researchers noted that under pathophysiological conditions, clinical strains of *B. fragilis* may be aerotolerant. This ability of strains is due to the presence of the following antioxidant enzymes in their cells: catalase, superoxide dismutase, peroxidase. Superoxide dismutase also protects bacteria from phagocytosis. Under aerobic conditions, *B. fragilis* induces expression of a large number of genes encoding enzymes of the oxygen-detoxification enzymatic and non-enzymatic systems (thioredoxin-dependent peroxidase, alkyl hydroperoxide reductase, fumarate reductase, non-heme ferretin, gem ferritin, etc.).

Histolytic enzymes produced by bacteroids (proteases, neuraminidase, hyaluronidase, nuclease, collagenase, etc.) cause destruction of immunoglobulins, complement components, matrix proteins (collagen, laminin, fibronectin, etc.), contributing to tissue necrosis and the spread of purulent process. Thus, protease destroys secretory antibodies (IgA) suppressing the immunity of the mucous membranes of the body. This enzyme also destroys complement factors inhibiting phagocytosis. Deoxyribonuclease breaks down DNA of cells, contributing to the abscess of affected tissues. Heparinase causes formation of the local blood clots, causes intravascular changes and tissue ischemia as a result of the heparin destruction. Beta-lactamase causes resistance to beta-lactam antibiotics (penicillins, cephalosporins) [3].

Pathogenicity of *B. fragilis* is also associated with the production of enterotoxin fragmentylisine (BFT - *B. fragilis* toxin). The latter has a general toxic effect on body tissues, causing synthesis of cytokines, as a result of which inflammation develops. Enterotoxin damages cytoskeleton of enterocytes, changes their secretory properties and causes degeneration of intestinal epithelial cells. BFT is a zinc metalloprotease, a secretory protein with a molecular weight of 20 kDa. It is encoded by a gene that is part of the pathogenicity island in the genome of *B. fragilis*. Just like in other bacteria,

pathogenicity islets are the genetic basis for the synthesis of pathogenicity factors in enterotoxigenic strains. Toxin-producing strains (ETBF), unlike non-pathogenic strains (NTBF - nontoxigenic *B. fragilis*) can produce 3 variants of enterotoxin. Synthesis of these toxins is encoded by the genes *btf-1, btf-2, btf-3.* Toxin destroys structural and functional contacts between intestinal epithelial cells, resulting in their exfoliation and hypersecretion of the fluid [16].

Thus, enterotoxin promotes penetration of the bacteria into deeper tissues and development of an inflammatory reaction, leading to appearance of the gastrointestinal tract diseases, sepsis, bacteremia, abscesses, and lung infection. However, it has been found that healthy people can be asymptomatic carriers of enterotoxin-positive strains.

Another anti-phagocytic factor is the ability of bacteroids to produce low molecular weight fatty acids. Thus, *B. fragilis* accumulates succinic acid, which inhibits phagocytic function of alveolar macrophages, disrupting their functional activity. *B. fragilis* produces various toxins and enzymes that can not only break down tissue structures and organs of a person, but also can suppress function of the immune system of a macroorganism. For example, *B.fragilis* heparinase is involved in the pathological activation of intravascular coagulation and promotes the formation of intravascular blood clots, enhancing tissue ischemia. Collagenase destroys the collagen structure of connective tissue and promotes the spread of purulent process [3].

Antibiotic resistance of *B. fragilis.* For treatment of infections caused by *Bacteroides spp*. metronidazole, carbapenems, combinations of β-lactams with β-lactamase inhibitors, clindamycin, moxifloxacin, cephalosporin are used. Sensitivity to these anti-anaerobic drugs depends on the type of microorganism, geographical location and on medical institutions. Recent years, worldwide resistance of bacteroids to various antimicrobials has increased, and resistance to several antibiotics, the so-called multiresistance, has also been observed [18, 19]. *Bacteroides fragilis* isolates have numerous resistance determinants, such as a drug resistance efflux pump, *cfiA* and *nimB* genes and activating insertion sequences, and some isolates may exhibit extensive drug resistance patterns. Frequency of multiresistance in *B. fragilis* is from 1.5 to> 18% and up to> 71% in *cfiA* and *nimB*-positive isolates [20].

It should also be noted that recent years there has been a decrease in the susceptibility of *B.fragilis* isolates to certain antibiotics in the world. For example, clindamycin resistance currently is 85% [21]. Resistance associated with the production of *β*-lactamases (penicillinases and cephalosporinases) to natural and semi-synthetic penicillins and cephalosporins is also currently approaching 100%.

Resistance of *Bacteroides spp* to fluoroquinolones over the past few years has increased from 1.5 to 12% [22].

Clinical strains of *Bacteroides spp* also show an increase in resistance to tetracyclines from 30% to 80% [16]. Genes that determine the resistance to tetracycline *(tet)* of gram-negative bacteria are often found in the Tn10 transposon, transmitted between large conjugative plasmids. Plasmid resistance to tetracycline is associated with decrease in its accumulation by the cell, reverse transport (in gram-negative ones, the *tetA – tetE, tetG* and *tetH* genes), intracellular inactivation *(tetX)*, and the protection of target ribosomes *(tetM or tetQ)*.

Most of the *tet* genes encode one of two mechanisms of tetracycline resistance: either an outflow of antibiotics or a ribosomal defense. Ribosomal protection involves protein synthesis similar to the elongation factor G. It interacts with the ribosome, not interfering with protein synthesis, but also preventing tetracycline from inhibiting this synthesis. In some types of bacteria, oxidative destruction of tetracycline was detected [10].

Carbapenem resistant isolates were described. Thus, studies conducted in Europe showed that over the past 20 years there has been an increase of imipenem resistance of *B. fragilis* from 0% to 1.2% in European countries [23]. Similar increase in imipenem resistance has been observed in the United States [24]. Studies in Korean hospitals in 2012 also showed that isolates of the *B. fragilis* show resistance to only 0–6% carbapenems [25]. Studies conducted in 2008-2012 in Taiwan also showed that 13.5% of *B.fragilis* isolates showed resistance to ertapenem [26].

In cases of carbapenems, the best-known resistance mechanisms include enzymatic modification of drugs, expression of silent resistance genes (*cfiA* for carbapenems) activated by (IS) inserts [27].

SydenhamT. V. et al. consider that complete identification of insertion sequence (IS) elements that carry promoter sequences in front of resistance genes seems to be necessary to further prediction of the resistance of the strain to antimicrobial agents [28].

The *cfiA* gene, which is usually chromosomal, encodes a synthesis of metallo-β-lactamase, which in turn gives the strain resistance to carbapenem [29]. So, studies at the Turkish University Hospital show that 27% of the resistant *B.fragilis* bacteria contained a *cfiA* gene [30].

Also, in recent years, resistance to metronidazole, which for many years was considered as traditional anti-anaerobic drug, has significantly increased (up to 50%). The mechanism of resistance to metronidazole is associated with specific genes. Namely, 9 *nim* genes (from *nimA* to *nimJ*) have been described in the literature for *B. fragilis* [31]. Metronidazole resistant *B. fragilis* strains had been reported in many countries, including Brazil [32] India [33], USA [34], and Hungary [35].

Thus, last decade there has been an increase in resistance to antimicrobial drugs, as well as an increase in prevalence of resistance genes to these drugs globally.

Mechanisms of antibiotic resistance development in bacteroids

Table 1 presents main mechanisms of antibacterial drugs action and development of a bacterial resistance to it.

Table 1. Mechanisms of antibacterial drugs action and developmet of a bacterial resistance to it [10]

Group of antibacterial drugs	Drugs	Mode of action	Mode of a resistance development
Beta-lactam antibiotics	Penicillin Cephalosporin, Monobactam, Carbepenem: imipenem, meropenem	Inhibit bacterial cell membrane formation by blocking cross-linking cell wall structures in penicillin-binding proteins (peptidoglycan synthetic enzymes)	Low permeability beta-lactamase, beta-lactamase modification
Lincosamides	Clindamycin	Inhibit transfer of amoni acids into the peptide chain of the 50S bacterial	Decreased ribosome binding (ribosomal RNA methylation). Low

		ribosome subunit; inhibits protein synthesis	permeability. Modifying Enzymes
Metronidazole		Destroys structure of nucleic acids	Changes activation mechanisms of drugs
Quinolones	Ciprofloxacin, Nalidixic acid	Blocks DNA synthesis DNA- gyrase, topoisomerase	Change of a target (DNA gyrase, topoisomerase). Low permeability. Active outflow

Currently, two chromosomal cephalosporinase genes have been described in *B. fragilis*. The first *cepA gene* encodes class 2e cephalosporinase. *CepA* gene product leads to resistance to most β-lactam antibiotics, with the exception of cefamycins, carbapenems and combinations of β-lactamase inhibitors. The second chromosomal β-lactamase gene *cfiA* (also known as *ccrA*) expresses a class of metallo-β-lactamases that confer *B. fragilis* resistance to all β-lactam antibiotics, including carbapenems [36].

Noticeably, *cfiA* gene is much more common (2.4–6.9%) in the chromosomes of clinical isolates of *B. fragilis*, than resistance to carbapenem (~ 1%) [37].

As indicated above, resistance to carbapenems in *B. fragilis* is associated with the production of metallo-β-lactamase with two Zn^{2+} ions in the active site encoded by the *cfiA* gene, which is sometimes in a silent state. Increase of the frequency of isolation of Ineperema resistant strains of *Bacteroides spp*. is preceded by an increase in the carriage of the *cfiA* gene. This is due to the ability of *cfiA*-positive strains to become resistant as a result of an insertion of a promoter in IS sequences (for example, IS1186, IS942) [38].

Nagy E. S. et al. suggested using the MALDI-TOF MS method for differentiating *B. fragilis* strains carrying the *cfiA* gene (group II) from those that do not carry it (group I), thereby making it easy to quickly distinguish between two groups of *B. fragilis* strains according to the presence of the *cfiA* gene. That is, the *cfiA* gene can only be found on the chromosomes of *B. fragilis* strains belonging to group II. In their work the authors showed that almost 100% carbapenem-resistant *Bacteroides* strains are *cfiA*-positive [36].

Wybo et al. showed that the use of MALDI Biotyper allows a clear separation of *cfiA*-positive and *cfiA*-negative *B. fragilis* strains. Thus, in their work, they succeeded in differentiating *cfiA*-positive (in an amount of 41) and *cfiA*-negative (in an amount of 207) *B. fragilis* strains [39].

Hence, it is important to carry out not only a phenotypic determination of a sensitivity of cultures to carbapenems, but also the identification of the *cfiA* gene using molecular genetic analysis methods.

Currently, it has been shown that there are two types of efflux pumps that are responsible for a multidrug resistance to antibiotics of *B.fragilis* strains. They are RND (resistance-nodulation division) and MATE (multiple drug and toxic outflow). *B. fragilis* evolved from a relatively susceptible bacterium into a pathogen that can currently be immune to most classes of antibiotics, even carbapenems and metronidazole. Overexpression of efflux pumps plays a significant role in the resistance of *B. fragilis* to antimicrobial agents, such as β-lactams, fluoroquinolones, tetracyclines, novobiocin, metronidazole [40].

Prospects of whole genome sequencing for prediction of antimicrobial drugs susceptibility. For majority of clinically significant bacterial pathogens phenotypic analysis of antimicrobial drugs susceptibility is relatively simple method that is based on well-established methods. Such methods include micro-dilution of agar and broth or disk diffusion, followed by further interpretation according to the manufacturer's instructions. Prediction of antimicrobial resistance (AMR) using whole genome sequences of clinical isolates in the nearest future is expected to reduce the time from the moment of sampling to final results (up to 8 hours) and can be implemented in clinical microbiology, by possibly completely eliminating phenotypic analysis [41]. For some types of microorganisms, the AMR prognosis based on whole genome sequencing (WGS) has already been confirmed, but for most clinically significant species, such confirmations have not yet been obtained. Since WGS-based assays cannot determine the minimum inhibitory concentration (MIC) or zone diameter, WGS approaches to AMR should be considered at the stage of detecting the presence or absence of genes

Therefore, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) currently recommends formations of a single database of all known resistance genes/mutations in order to ensure possibility to conduct analysis and measurement of comparative accuracy in different bioinformatics systems and tools. This database should be regularly updated, and it must strictly adhere to the minimum standards of inclusion of new resistance genes and mutations. Possibility of controlling nomenclature of resistance genes will be an important fuction of the centralized database. However, accurate prediction of resistance using WGS may be difficult due to insufficient knowledge of all genetic variations leading to a decrease in susceptibility to antimicrobial agents, as well as to the emergence of new resistance mechanisms due to altered gene expression (eg, encoding efflux pumps) [42].

As described above, *Bacteroides fragilis* is the most commonly isolated anaerobic bacterium from non-fecal clinical specimens. However, only a small number of their complete genomes are available in public databases [43]. Many authors (Köser, C.U. and others) believe that the regular use of WGS in clinical and research laboratories promises revolutions in identification, typing, testing a sensitivity to antimicrobials and determination of pathogenicity of potentially pathogenic microorganisms [44].

CONCLUSIONS

The study of genomic structure of *B. fragilis* can be used both for the further study of pathogenesis of bacteroids and for the development of new drugs to treat anaerobic infections.

The study of the pathogenic potential of *B. fragilis* expands the idea of their clinical significance in intra-abdominal diseases and helps to understand the pathogenetic mechanisms of these infections development.

In recent years there has been an increase in resistance of bacteroids to antimicrobial agents: penicillins, cephalosporins, tetracyclines and other antibiotics, which makes them ineffective in the treatment of anaerobic infections caused by *B. fragilis.*

Carbapenemes, nitroimidazoles, and inhibitor-resistant β-lactams are the drugs of choice for the treatment of bacterioid infections.

Full genome sequencing has an important role to play in predicting antimicrobial susceptibility and can be implemented in clinical microbiology by eliminating time-consuming phenotypic analyses.

Acknowledgements

This work was supported by the Ministry of Education and Science Republic of Kazakhstan (grant AP05130984 «Study and assessment of the sensitivity to broad spectrum antibiotics of *Bacteroides fragilis* group bacteria in patients with intraabdominal anaerobic infections» for 2018-2020).

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BACTEROIDES FRAGILIS-ТІҢ ПАТОГЕНДІКТІК ЖӘНЕ АНТИБИОТИКАЛЫҚ ТҰРАҚТЫЛЫҚ ФАКТОРЛАРЫ

Қожахметова С.С., Жолдыбаева Е.В., Мухтарова К. Е., Раманкулов Е.М.

Ұлттық биотехнология орталығы
Қорғалжын тас жолы, 13/5,Нұр-Сұлтан қаласы, 010000, Қазақстан
sskozhakhmetova@gmail.com

ТҮЙІН

Бұл мақалада жіктеудің заманауи тұжырымдамалары, геномдық құрылым (инверттелген аймақтар, қозғалмалы генетикалық элементтер, плазмидалар, жұмылдырылған және біріктірілген транспозондар қарастырылады), патогенділік факторлары (адгезиндер, түрлі ферменттер, токсиндер, атап айтқанда энтеротоксин фрагилизин BFT – *B. Fragilis* toxin - туралы мәліметтер келтірілген), сонымен қатар олардың метаболиттерінің патогенділік көрінісіндегі рөлі қарастырылады. Клиникалық *B. fragilis* штаммдарындағы антибиотикке төзімділіктің бүкіл әлемдік таралуы туралы мәліметтер келтірілген, олардың дәріге төзімділігі даму механизмдері қарастырылған, антибиотикке төзімділікті дамытудағы *cfiA, tet, nim* гендерінің рөлі ашылған. *B. fragilis* штаммдарын карбапенемге төзімді генді екі топқа (*cfiA* генін алып жүретін және алып жүрмейтін) бөлу қабілетімен ажырату үшін MALDI-TOF MS (матрицалық-лазерлік десорбция-ионизация уақыты бойынша ұшудың масс-спектрометриясы) әдісін қолдану туралы мәліметтер келтірілген. *B. fragilis* клиникалық штаммдарында көп төзімділіктің пайда болу негіздері де қарастырылған. Сондай-ақ, микробқа қарсы тұрақтылықты болжауда геномдардың толық тізбектелу перспективалары көрсетілген. Қазір *B. fragilis* кеңінен қолданылатын антимикробтық агенттерге төзімділігін арттыруға көп көңіл бөлінетіні көрсетілген, бұл антимикробтық терапияны таңдауда үлкен маңызға ие.

Негізгі сөздер: *Bacteroides fragilis*, патогендік факторлары, антибиотиктерге төзімділік, микробқа қарсы терапия, дәрі-дәрмектерге төзімділік механизмдері, антибиотиктерге төзімділік гендері.

ФАКТОРЫ ПАТОГЕННОСТИ И УСТОЙЧИВОСТИ К АНТИБИОТИКАМ У *BACTEROIDES FRAGILIS*

Кожахметова С.С., Жолдыбаева Е.В., Мухтарова К. Е., Раманкулов Е.М.

Национальный центр по биотехнологии
Кургальжинское шоссе, 13/5, г Нур-Султан, ,010000, Казахстан
sskozhakhmetova@gmail.com

АБСТРАКТ

В настоящей статье приведены современные представления о классификации, геномной структуре (рассмотрены инвертированные регионы, мобильные генетические элементы, плазмиды, мобилизуемые и конъюгированные транспозоны), факторах патогенности (адгезинах, различных ферментах, токсинах, в частности, приведены данные об энтеротоксин фрагилизине BFT – *B. fragilis* toxin), а также рассмотрена роль их метаболитов в проявлении патогенности. Приведены данные, по проблеме распространенности в мире, антибиотикорезистентности у клинических штаммов *B. fragilis*; рассмотрены механизмы развития их лекарственной устойчивости, раскрыта роль *cfiA, tet, nim* генов в развитии антибиотикорезистентности. Приведены данные по применению MALDI-TOF MS (матрично-активированная лазерная десорбционно-ионизационная времяпролетная масс-спектрометрия) метода для различения штаммов *B.fragilis* по способности нести карбапенемустойчивый ген, на две группы (несущие и не несущие *cfiA* ген). Рассмотрены также основы появления мультирезистентности у клинических штаммов *B. fragilis*. Также приведены перспективы полногеномного секвенирования в прогнозировании устойчивости к противомикробным препаратам. Показано, что в настоящее время, все чаще внимание исследователей обращено на повышение устойчивости *B. fragilis* к широко применяемым противомикробным препаратам, что имеет большое значение при выборе адекватной антимикробной терапии.

Ключевые слова: *Bacteroides fragilis*, факторы патогенности, антибиотикорезистентность, антимикробная терапия, механизмы развития лекарственной устойчивости, гены устойчивости к антибиотикам.