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Original Article

STUDY OF GENE EXPRESSION IN RESPONSE TO SERIAL EXPOSURE TO MEROPENEM IN *BACTEROIDES FRAGILIS*

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ABSTRACT

Antibiotic resistance is a major global health concern, and inappropriate antibiotic use contributes significantly to the development of resistance in pathogens. *Bacteroides fragilis*, an anaerobic bacterium, is commonly treated with β-lactam antibiotics like meropenem. *B. fragilis* possesses various antibiotic resistance mechanisms, including enzymatic modification of antibiotics, efflux systems, and reduction of cell membrane permeability. The primary mechanism of carbapenem resistance in *B. fragilis* is linked to the production of a metallo-β-lactamase encoded by the *cfiA* gene. However, this gene is frequently inactive and requires activation by insertion elements.

The study aimed to explore the expression of specific genes in *B. fragilis* associated with different metabolic pathways in response to exposure to sub-inhibitory concentrations of meropenem. The study used *B. fragilis* strain BFR KZ01, obtained from a patient with appendicitis and peritonitis. Serial exposure to meropenem was conducted, and gene expression was analyzed using quantitative RT-PCR. Significant and long-lasting alterations in gene expression patterns were observed in *B. fragilis* following exposure to meropenem, even after removal of the antibiotic. Genes such as *cfiA*, *oxyR*, and *Ddl* showed heightened expression levels even after discontinuation of meropenem.

The study discussed the implications of gene expression changes induced by meropenem exposure, highlighting the role of oxidative stress response (*oxyR*), D-Ala-D-Ala ligase (*Ddl*), and carbapenemase (*cfiA*) genes in antibiotic resistance mechanisms. The study concluded that exposure to meropenem induced lasting alterations in gene expression in *B. fragilis*, contributing to antibiotic resistance. Understanding these mechanisms is crucial for developing strategies to combat antibiotic resistance.

Key words: *Bacteroides fragilis,* antibiotic resistance, gene expression, meropenem, β-lactamase, *cfiA* gene

INTRODUCTION

The emergence of life-threatening infections resistant to antimicrobial treatments is currently the world's most pressing issue. Microbial resistance is one of the top ten worldwide threats to human health, according to the World Health Organization (WHO). The primary contributor to the development of drug resistance in pathogens is the inappropriate and excessive use of antimicrobial drugs.

In comparison to other anaerobes, *Bacteroides fragilis* possesses a variety of antibiotic resistance mechanisms. In clinical practice, *B. fragilis* infections are commonly treated with β-lactam medicines, particularly carbapenems.

Carbapenems, a type of β-lactam antibiotic, are effective against a wide variety of pathogens, including both aerobic and anaerobic gram-positive and gram-negative bacteria. Carbapenems function by inhibiting the synthesis of microorganism cell walls: they attach to penicillin-binding proteins and prevent the cell wall from being formed. The following are the primary mechanisms contributing to antibiotic resistance in bacteria include enzymatic modification of antibiotics or their targets, which also leads to resistance [1, 2], efflux systems that remove antibiotics from within the cell [3, 4], and reduction of cell membrane permeability as a result of mutations in porins, protein channels in the outer membrane of gram-negative bacteria that are essential for the transport of various substances [1].

Pathogens develop characteristics such as multidrug resistant, high resistance, and pan resistance are formed when distinct resistance mechanisms and resistance genes to several drugs combine [5–7]. Enzymatic breakdown of the β-lactam ring by enzymes called β-lactamases is the main method by which gram-negative bacteria resist β-lactam antibiotics. Most genetic elements carrying β-lactamase genes are mobile, facilitating their rapid and widespread proliferation among microbial populations.

The mechanism of carbapenem resistance in *B. fragilis* is linked to the production of a metallo-β-lactamase that contains two *Zn2+* ions in its active center and encoded by the *cfiA* gene [8]. However, this gene is frequently inactive. The rise in carbapenem-resistant variants of *B. fragilis* precedes the increase in the number of strains carrying the *cfiA* gene. The *cfiA* genes in positive strains of *B. fragilis* can be activated by insertion elements IS1186, IS942, and IS4351. This activation occurs when these elements insert ahead of the promoter gene.

The development of alternative antimicrobial drugs and effectively managing resistance require a comprehensive understanding of the processes behind antimicrobial resistance.

The aim of this study was to explore the expression of specific *B. fragilis* genes, which are associated with different metabolic pathways and involved in the response of anaerobes, when exposed to a sub-inhibitory concentration of meropenem.

MATERIALS AND METHODS

Bacterial strain and culture conditions

The study focus was the culture of *B. fragilis* BFR KZ01,

which was obtained in 2018 from a patient who had been diagnosed with acute gangrenous-perforated appendicitis and peritonitis.

Following an extended period of storage at -70°C in glycerol, the culture was recovered by seeding it onto (Bile Esculin Agar, Conda). Multiple media were used for the further cultivation, including Brain Heart Infusion broth (Himedia, India) and Gifu Anaerobic Medium (GAM) (Himedia, India), which were enhanced with 0.1% L-cysteine [9], 5 µg/mL of vitamin K [10], and 0.5% hemin. The wild strain and subcultures were grown in anaerobic medium for 48 hours at 37°C. The growth characteristics of a *B. fragilis* culture were investigated using GAM broth.

Determination of meropenem sub-inhibitory concentration

In accordance with CLSI (the Clinical and Laboratory Standards Institute standards) [11], sensitivity to meropenem was determined using serial dilutions in broth. Every measurement was carried out using sterile coverslips on 24-well immunoassay plates with a flat bottom (Corning). In order to accomplish this, 1% of the *B. fragilis* bacterial culture, or 1 McFarland standard, was added to Brucella broth (Himedia) which contained meropenem at various concentrations ranging from 0.06 to 64 µg/mL. The inoculum was transferred into the plate wells carrying meropenem dilutions around 15 minutes of the preparation period.

The growth of the microorganism in the presence of antibiotic and the growth of the culture in the cell without antibiotic were compared using spectrophotometric recording at 600 nm using a Cytation 5 spectrophotometer (Cell imaging multi-mode reader, Boiotek). The minimum inhibitory concentration (MIC) was determined after 48 h of cultivation. The minimum concentration providing complete suppression of visible growth of the strain under study was interpreted as the MIC. The sub-inhibitory concentration of meropenem was taken as 0.5 MIC.

Production of subcultures both with and without the antibiotic meropenem

Anaerobic conditions were maintained at 37°C for the growth of bacteria on Brain Heart Infusion broth (Himedia, India) supplemented with 0.1% L-cysteine, 0.5% hemin, 5 µg/ml vitamin K, and 1 µg/ml meropenem. The cultures expanded until the mid-logarithmic period. For eight days, *in vitro* subculture selection with or without meropenem was carried out at 48-hour intervals. All subcultures were identified using MALDI-TOF mass spectrometry. After the second stage of culture in the presence of meropenem, subculture BrFM2 was selected from the initial *B. fragilis* strain (BrFM0), and subculture BrFM4 was selected following the fourth step of co-culturing the bacteria and antibiotic. Additionally, when the subculture, BrFM4, was cultivated without antibiotics, subculture BrFM5 was chosen, and subculture BrFM8 was additionally acquired from the fourth subculture when the antibiotic was not used (Table 1). A 10% inoculum was added to each subculture to prevent the buildup of potentially dead cells.

Quantitative RT-PCR assay

RNA was extracted by using a RNeasy Protect Bacteria Mini kit (Qiagen, Hilden, Germany). cDNA for quantitative Real Time PCR (qPCR) experiments were prepared using with 100 ng of RNA template and using M-MuLV -RH - genetically modified reverse transcriptase (revertase) of mouse leukemia virus (M-MuLV) (Biolabmix kit, Russian). Thermocycling conditions consisted of an initial denaturation of 5 min at 95°C, followed by 35 cycles of 95°C for 10 s, 55°C for 20 s, and 72°C for 30 s. The reaction mixture contained 12.5 ml SYBR Blue (2x) (Biolabmix, Russian), 1.0 ml of forward primer, 1.0 ml of reverse primer, 9.5 ml H_2O and 1.0 ml of cDNA template per well. All gene-specific primers were designed manually by employing the Vector NTI 10.0 software [12], and details of gene specific primer sequences are provided in Table 2. GroL was amplified to serve as a comparator gene, against which expression of the genes of interest were normalized. qPCR was performed using BioRad CFX96 Touch Real Time PCR, BioRad.

The relative level of gene expression was determined using Bio-Rad CFX Manager™ 3.0 Software (Bio-Rad Laboratories Inc., USA). For the reliability of the experiment, the expression of each investigated gene was performed in three repetitions.

RESULTS

The three *cfiA, oxyR,* and *ddl* genes expression patterns in *B. fragilis* were investigated in response to meropenem drug exposure, and the results demonstrated significant, long-lasting alterations in the bacteria gene expression patterns.

In this regard, the results we obtained demonstrate that the strain that experienced selective meropenem pressure (SIC) underwent significant changes in gene expression patterns,

Table 1. Information data of the isolates used in this study

Samples (subcultures)	Description
BrFM0	The wild strain *B. fragilis* BFR KZ01
BrFM2	The sample, obtained from a wild strain (BrFM0), following a second subculturing with meropenem. The antibiotic volume is 0.5 µg/ml. OD – 0,575. 48 h.
BrFM4	The sample, obtained from a wild strain (BrFM0), following a fourth subculturing with meropenem. The antibiotic volume is 0.5 µg/ml. OD – 0,565. 48 h.
BrFM5	The s sample, obtained from BrFM4 strain, following the first subculturing without meropenem. OD – 0,577. 48 h.
BrFM8	The sample, obtained from BrFM4 strain, following a fourth subculturing without meropenem. OD – 0,553. 48 h.

Table 2. Gene-specific primers, oligonucleotide sequences and all function of gene

Primers	Sequence 5'-3'	Tm	Product size, bp	Protein	Molecular function	Biological process
cfiA_F	CTCCATGCTTTTC-CCTGTCG	58.91	200	β-lactamase	- β-lactamase activity; - zinc ion binding	- antibiotic catabolic process; - response to antibiotic;
cfiA_R	CGTCATTGATCGGT-GTGTCC	59.00				
ddl_F	TAGAAATGGAAG-GTCGGCGT	59.10	132	D-alanine-D-alanine ligase	- D-alanine-D-alanine ligase activity; - ATP binding; - metal ion binding;	- regulation of cell shape; -peptidoglycan biosynthetic process; - cell wall organization;
ddl_R	TCGAAATAGCCCT-GCAAACG	58.92				
oxyR_F	TGCCCTACTGC-CATTGGTAA	59.00	232	redox-sensitive transcriptional activator	- cis-regulatory region sequence-specific DNA binding; - DNA-binding transcription factor activity;	-DNA damage response; - regulation of DNA-templated transcription; - response to nitrosative stress; - response to oxidative stress;
oxyR_R	GAATGTCGGGC-GTCTTCATC	59.07				
groL_F	CGGTTATCGGTA-AACTGATTGC	59.01	498	chaperonin	- ATP binding; - ATP-dependent protein folding chaperone; - isomerase activity; - unfolded protein binding;	- protein refolding;
groL_R	GATTTAGTAGCAG-CAATCTGAGC	58.03				

even when growth situations were returned to the starting point drug-free condition (Figure 1, Table 3).

As illustrated in Figure 1 and outlined in Table 3, we observed a heightened expression level of the targeted genes even subsequent to discontinuation of the meropenem drug. Differences in expression levels are observed across all three genes in various samples, indicating potential regulation or response to the culturing conditions (Table 3). Samples BrFM5 and BrFM8 consistently show higher expression levels to other samples for all three genes. The variability in SEM values reflects the precision of the sample mean estimates. Lower Cq values indicate higher initial RNA concentrations in the samples.

This suggests that even when growth conditions are restored to the original drug-free condition, the recovered strain exhibits significant changes in whole-gene expression patterns.

This analysis offers a summary of the gene expression patterns identified in the data, which can be explored further to comprehend the biological implications of these expression patterns in *B. fragilis* strains under diverse culture conditions.

DISCUSSION

A description of the *B. fragilis* BFR_KZ01 strain with multiple drug resistance was previously published in the Saniya Kozhakhmetova et al. (2021) article [13]. Investigating potential bacterial genes associated with resistance mechanisms involved in the human organism's reaction to carbapenems, particularly meropenem, was one of the study objectives. The *cfiA/ccrA* family, *ddl, oxyR*, as well as *nimB, tetQ*, and *gyrA* genes, which confer resistance to metronidazole, tetracycline, and ciprofloxacin, have been determined to be present in the *B. fragilis* BFR_KZ01 strain according to whole-genome analysis.

Recent research has shown that reactive oxygen species (ROS) have a role in antibiotic resistance. *OxyR*, one of the major regulators, becomes activated in response to oxidative stress. It undergoes structural alterations when exposed to hydrogen peroxide and superoxide radicals [14].

According to the radical-based approach, secondary ROS production plays a significant factor in how all bactericidal drugs work to destroy bacteria. The drug interaction with its target alters the metabolic state of the cell, leading to hyperstimulation of the electron transport chain and increased generation of superoxide, which is a typical byproduct of aerobic respiration [15,16]. The generation of ROS and reactive metabolic byproducts is a secondary consequence of exposure to

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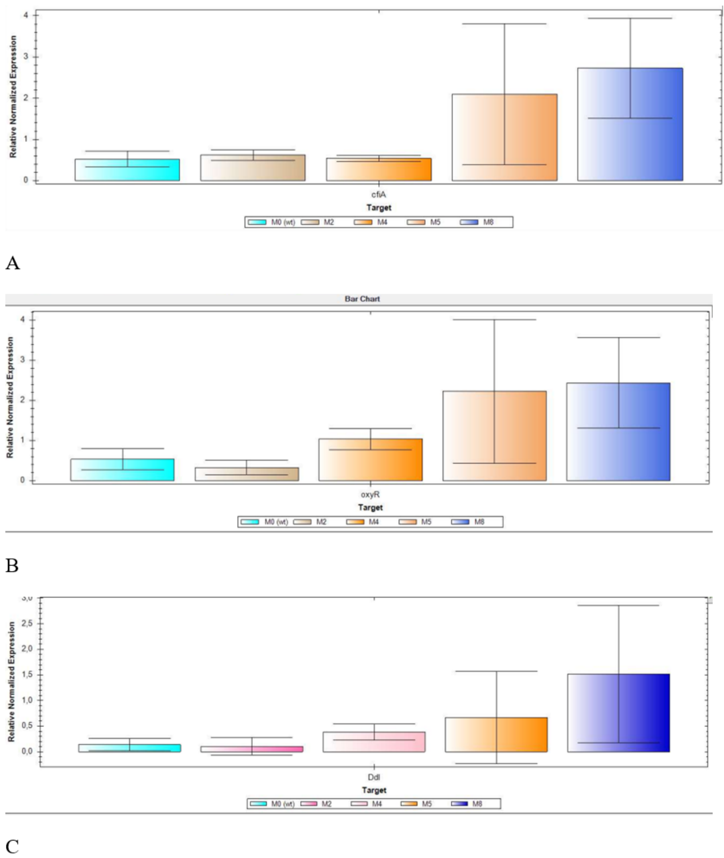

Figure 1. qPCR boxplot of gene expression patterns: *cfiA* (A), *oxyR* (B), *ddl* (C) of *B. fragilis*.

Table 3. Gene expression data for *B. fragilis* strains

Target	Sample	Expression	Expression SEM	Corrected Expression SEM	Mean Cq	Cq SEM
cfiA	BrFM0	0,52400	0,19318	0,19318	18,73	0,73789
	BrFM2	0,61856	0,13116	0,13116	18,54	0,47368
	BrFM4	0,53956	0,07762	0,07762	18,82	0, 31236
	BrFM5	2,09701	1,70664	1,70664	19,31	1,50542
	BrFM8	2,72673	1,21607	1,21607	17,16	0,73715
oxyR	BrFM0	0,53746	0,26094	0,26094	28,41	0,94333
	BrFM2	0,33005	0,18398	0,18398	29,13	1,16256
	BrFM4	1,03956	0,26299	0,26299	27,58	0,52018
	BrFM5	2,22627	1,79282	1,79282	28,90	1,30977
	BrFM8	2,43586	1,12991	1,12991	26,98	0,69856
Ddl	BrFM0	0,13982	0,12077	0,12077	24,29	1,17542
	BrFM2	0,10603	0,16923	0,16923	25,63	2,14370
	BrFM4	0,38428	0,15770	0,15770	23,09	0,58640
	BrFM5	0,66708	0,90201	0,90201	24,70	1,65395
	BrFM8	1,51858	1,34420	1,34420	21,45	0,97186

bactericidal antibiotics, which speeds up the death of bacteria. The excess generation of ROS leads to oxidation of guanine to 8-oxo-guanine and affects the pool of nucleotides, proteins, lipids, and DNA [17]. In addition to being deadly, ROS can speed up the pace of mutation [18]. ROS defense mechanisms are induced by previously acquired resistance to a first bactericidal medication. Compared to susceptible cells, these cells create less ROS when exposed to MIC doses of antibiotics, which speeds up adaptation to a second bactericidal drug.

Wenxi Qi discussed the function of ROS in antibiotic resistance, determine out if oxygen and ROS affect *de novo* acquisition of antibiotic resistance, the development of resistance resulting from exposure to non-lethal doses of antibiotics was studied in *E. coli* wildtype and Δ*oxyR* strains under aerobic and anaerobic conditions [19].

Additionally, studies such as those conducted by Wenxi Qi provide insights into the complex interplay among ROS, an-

tibiotic exposure, and the development of resistance in bacterial populations.

D-Ala-D-Ala ligase, encoded by *ddl* genes, is responsible for the synthesis of a dipeptide, D-Ala-D-Ala, an essential precursor of bacterial peptidoglycan [20]. The composition of peptidoglycan in lactic acid bacteria determines their resistance to vancomycin. Vancomycin poorly attaches to peptidoglycan that ends in D-alanyl-D-lactate, but it strongly binds to peptidoglycan ending in D-alanyl-D-alanine (D-Ala-D-Ala), leading to resistance or sensitivity to vancomycin, respectively. The enzyme responsible for creating these peptidoglycan precursors is dipeptide ligase (*ddl*). The research shows that introducing dipeptide ligase into vancomycin-resistant Lactobacilli increases their susceptibility to vancomycin in a manner dependent on dosage, and it counteracts the presence of a native D-Ala-D-Ala dipeptidase [21].

There is currently no available literature discussing the investigation of the *ddl* gene and its involvement with *B. fragilis* in the development of resistance mechanisms.

The *cfiA* gene is responsible for conferring high-level carbapenem resistance in *B. fragilis,* facilitated by a metallo-β-lactamase [22, 8]. This gene is prevalent within the *B. fragilis* population, with a distinct subgroup identifiable through molecular techniques. For *B. fragilis* to exhibit significant carbapenem resistance, an insertion sequence (IS) element is essential, serving to enhance gene expression through a robust promoter [23,24].

The prevalence of *B. fragilis* carrying the *cfiA* gene varies worldwide, ranging from 7.6% to 38.9% [25-29]. Additionally, the occurrence of *cfiA*-positive isolates falls within the range of 4.1% to 9.4% [24, 30-32]. The *cfiA* gene is present in a subset of *B. fragilis* known as division I and II, which could be regarded as distinct genospecies [33, 34]. Division II isolates possess a silent *cfiA* gene that can become overexpressed by an insertion of a mobile genetic element as a promoter located upstream of *cfiA* and thus develop a phenotypic resistance to carbapenems [28, 35]. However, the carbapenem resistance of *B. fragilis* is more complicated: strains without an IS element have a silent *cfiA* gene and have low carbapenem MICs (<1 μg/ml), IS-activated *cfiA*-positive strains have high carbapenem MICs (≥ 16 μg/ml) and *cfiA*-positive strains with an inactive IS element have elevated carbapenem MICs (>2 μg/ml) [23, 28, 36-38].

The presence of a silent *cfiA* gene suggests a level of genetic complexity in *B. fragilis* strains, where the potential for resistance development exists even without active expression of the carbapenemase gene. This highlights the importance of considering silent *cfiA* genes in understanding the overall resistance profile of *B. fragilis* strains [39].

CONCLUSION

It is important to acknowledge that this study specifically focused the response of *B. fragilis* to meropenem exposure, limiting the direct applicability of the results to other antibiotics or bacteria. However, the findings do provide valuable insight into how bacteria adapt to antibiotic exposure, potentially helping inform the development of novel strategies to address antibiotic resistance. The enduring impact of meropenem exposure on bacterial gene expression is evident.

Furthermore, the study found that the strains selected post- meropenem removal exhibited functional similarities to strains selected after drug exposure, indicating that the gene expression changes induced by meropenem persisted even after the antibiotic was removed.

In summary, these analyzed results suggest that exposure to antibiotics like meropenem can induce lasting alterations in gene expression that contribute to antibiotic resistance. This highlights the significance of comprehending the mechanisms driving antibiotic resistance and developing effective strategies to combat it.

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ИЗУЧЕНИЕ ЭКСПРЕССИИ ГЕНОВ В ОТВЕТ НА ПОСЛЕДОВАТЕЛЬНОЕ ВОЗДЕЙСТВИЕ МЕРОПЕНЕМОМ НА *BACTEROIDES FRAGILIS*

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АННОТАЦИЯ

Устойчивость к антибиотикам является одной из основных проблем глобального здравоохранения, а неправильное использование антибиотиков вносит значительный вклад в развитие устойчивости патогенных микроорганизмов. *Bacteroides fragilis*, анаэробная бактерия, обычно лечится β-лактамными антибиотиками, такими как меропенем. *B. fragilis* обладает различными механизмами устойчивости к антибиотикам, включая ферментативную модификацию антибиотиков, системы эффлюкса и снижение проницаемости клеточной мембраны. Основной механизм устойчивости к карбапенемам у *B. fragilis* связан с выработкой металло-β-лактамазы, кодируемой геном *cfiA*. Однако этот ген часто неактивен и требует активации с помощью инсерционных элементов.

Цель исследования - изучить экспрессию специфических генов *B. fragilis*, связанных с различными метаболическими путями, в ответ на воздействие субингибирующих концентраций меропенема. В исследовании использовали штамм *B. fragilis* BFR KZ01, полученный от пациента с аппендицитом и перитонитом. Влияние меропенема на субкультуры *B. fragilis (культивируемые с интервалом 48 часов) изучали*, анализируя экспрессию генов с помощью количественной RT-PCR. После воздействия меропенема на *B. fragilis* наблюдались значительные и длительные изменения в экспрессии генов, даже после отмены антибиотика. Такие гены, как *cfiA*, *oxyR* и *ddl*, демонстрировали повышенный уровень экспрессии даже после прекращения приема меропенема.

В исследовании было обсуждено изменение экспрессии генов, вызванных воздействием меропенема, и участие генов ответа на окислительный стресс (*oxyR*), D-Ala-D-Ala лигазы (*ddl*) и карбапенемазы (*cfiA*) в механизмах устойчивости к антибиотикам. Этот экспериментальный анализ подтвердил, что воздействие меропенема вызывает устойчивые изменения в экспрессии генов у *B. fragilis*, способствуя развитию антибиотикорезистентности. Понимание этих механизмов имеет решающее значение для разработки стратегий борьбы с антибиотикорезистентностью.

Ключевые слова: *Bacteroides fragilis,* антибиотикорезистентность, экспрессия гена, меропенем, β-лактамаза, ген *cfiA*

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BACTEROIDES FRAGILIS МЕРОПЕНЕМНІҢ БІРТІНДЕП ӘСЕР ЕТУІНЕ ЖАУАП РЕТІНДЕ ГЕН ЭКСПРЕССИЯСЫН ЗЕРТТЕУ

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ТҮЙІН

Антибиотикке төзімділік ғаламдық денсаулық сақтау ұйымдарының негізгі мәселесі болып табылады, ал антибиотиктерді тиімсіз қолдану патогенді микроорганизмдердің төзімділігінің дамуына айтарлықтай ықпал етеді. *Bacteroides fragilis*, анаэробты бактерия, әдетте меропенем тәрізді β-лактамды антибиотиктермен емделінеді. *B. fragilis* антибиотикке деген төзімділіктің әртүрлі механизмдеріне ие, сонын ішінде антибиотиктердің ферментативті модификациясы, эффлюкс жүйесі мен жасуша мембранасының өткізгіштігін төмендете алады. *B. fragilis* бактериясының карбапенемге төзімділігінің негізгі механизмі *cfiA* генімен кодталатын, металло-β-лактамазаны өндірумен байланысты болып келеді. Алайда, бұл ген көп жағдайда белсенді емес және кірістіру элементтері арқылы белсендіруді қажет етеді.

Зерттеу жұмысының мақсаты – меропенемнің субингибирлеуші концентрацияларының әсеріне жауап ретінде әртүрлі метаболикалық жолдармен байланысты *B. fragilis* спецификалық гендерінің экспрессиясын зерттеу. Зерттеу жұмыстарында соқырішек және перитонитпен ауыратын науқастан бөлініп алынған *B. fragilis* BFR KZ01 штаммы қолданылды. Меропенемнің сериялық әсері жүзеге асырылды, гендердің экспересииясы сандық RT-PCR көмегімен сарапталды. *B. fragilis*-ке меропенеммен әсер еткеннен кейін гендердің экспрессиясында антибиотикті алып тастағаннан кейін де, мәнді және ұзаққа созылған өзгерістер бақыланды. *CfiA*, *oxyR* және *ddl* тәрізді гендер меропенемді енгізуді тоқтатқанан кейін де экспрессияның жоғарғы дәрежесін көрсетті.

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Зерттеу барысында меропенем әсерімен туындаған ген экспрессия өзгерісінің салдары талқыланды, антибиотикке төзімділік механизмдерінде тотығу стресс реакциясы (*oxyR*), D-Ala-D-Ala лигаза (*ddl*) мен карбапенемазаға (*cfiA*) әсер етуде гендердің рөлі белгіленді. Берілген тәжірбиелік сараптама қорытындысы бойынша, антибиотикке төзімділік жағдайын дамытуына мүмкіндік беру арқылы, меропенемнің әсері *B. fragilis* гендер экспрессиясының тұрақты өзгерісін туыдыратыны нақтыланды. Бұл механизмдерді түсіну антибиотикке төзімділік мәселесімен күресу стратегиясын әзірлеу үшін өте маңызды.

Негізгі сөздер: *Bacteroides fragilis,* антибиотикке төзімділік, ген экспрессиясы, меропенем, β-лактамаза, *cfiA* гені