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<https://doi.org/10.70264/jbr.v1.3.2025.1>CURRENT PERSPECTIVES ON MULTI-OMICS STUDIES OF BACTERIA FROM THE
BACTEROIDES GROUPSaniya Kozhakhmetova¹, Pavel Tarlykov¹, Dina Bayanbek², Elena Zholdybayeva^{1*}¹National Center for Biotechnology of the Ministry of Health of the Republic of Kazakhstan, Astana, Kazakhstan²L.N. Gumilyov Eurasian National University, Astana, Kazakhstan*Correspondence: Zholdybayeva Elena, zholdybayeva@biocenter.kz

ABSTRACT

This review discusses multi-omics (genomic, transcriptomic, and proteomic) approaches for studying bacteria of the *Bacteroides* spp. group, which are the most common anaerobes in the human colon and are responsible for over half of all intra-abdominal anaerobic infections. These multi-omics approaches have enabled the identification of virulence factors, antimicrobial resistance genes, and other functional elements of the *Bacteroides* genome. This information is crucial for understanding the pathogenic potential of these bacteria and their role in the development of anaerobic infections. This review examines the transcriptional response of *Bacteroides* after exposure to sub-inhibitory concentrations of antimicrobial drugs, as well as the main methods of proteomic analysis and achievements in studying the *Bacteroides* proteome. Overall, the modern perspectives of multi-omics studies on *Bacteroides* emphasize the possibility of integrating different omics approaches for a more comprehensive understanding of their biology, functional characteristics, and ecological roles in the gut ecosystem.

Keywords: *genomics, transcriptomics, proteomics, sub-inhibitory concentrations, carbapenems, Bacteroides.*

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1 INTRODUCTION

Bacteroides spp. is the dominant colonizers of the mammalian large intestine [1]. These obligate anaerobic Gram-negative bacteria are major contributors to metabolism and are capable of breaking down various polysaccharides derived from dietary fibers and host mucus, thereby facilitating nutrient absorption by the intestinal epithelium [2]. Furthermore, intestinal *Bacteroides* spp. protects their hosts from intestinal infections by stimulating the development of the immune system and providing resistance to pathogen colonization [3, 4].

Currently, over 70 species are recognized in the genus *Bacteroides*. This genus varies in many aspects, including genetics, physiological characteristics, and ecological niches. These differences affect the metabolic abilities of bacteria, enabling them to utilize diverse substrates for energy and growth. Some *Bacteroides* species are known for their ability to ferment glycans, whereas others specialize in utilizing specific organic compounds such as bile acids. The systems biology approach allows for a comprehensive understanding of the complex interactions between *Bacteroides* species and antimicrobial agents (or other factors) and provides insights into the underlying molecular mechanisms of bacterial resistance. Several studies have incorporated genomics, transcriptomics, and proteomics data to shed light on the intricate networks

and regulatory pathways involved in antibiotic resistance. As it may be inferred, most of the published research is focused on the clinically relevant *Bacteroides fragilis* group. *Bacteroides fragilis* is a prevalent anaerobic bacterium often implicated in infectious processes.

2 MATERIALS AND METHODS

2.1 Source Material

This review is based on previously published scientific literature focusing on *Bacteroides* spp., particularly studies utilizing genomic, transcriptomic, and proteomic (multi-omics) approaches. The review includes data obtained from both experimental research and comprehensive reviews, highlighting key findings on the virulence, antimicrobial resistance, and functional genomics of *Bacteroides* species.

2.2 Data Sources and Search Strategy

The literature search was conducted using the following scientific databases: Web of Science Core Collection, PubMed, and Google Scholar. More than 59 relevant articles were selected, comprising original research papers, systematic reviews, and book chapters published in leading international and regional journals. The review includes literature published during the period from 2002 to 2023.

The selection criteria focused on studies related to:

- Multi-omics analyses (genomics, transcriptomics, proteomics) of *Bacteroides* spp.;
- Identification of virulence and resistance genes;
- Transcriptional response to sub-inhibitory concentrations of antimicrobial agents;
- Gut microbiome interactions and ecological functions.

2.3 Research Tools and Keywords

The primary keywords and search terms used for literature retrieval included: “*Bacteroides* spp.”, “multi-omics”, “genomics”, “transcriptomics”, “proteomics”, “antimicrobial resistance”, “sub-inhibitory concentrations”, “gut microbiome”, “anaerobic infections”. Search filters were applied to focus on peer-reviewed publications in English, with particular attention to articles involving experimental omics methodologies and clinical relevance.

3 THE GENETIC BASIS OF *BACTEROIDES* SPP. RESISTANCE TO CARBAPENEMS

One of the characteristic representatives of the genus *Bacteroides* is *Bacteroides fragilis*. It is a commensal species that under certain conditions can cause severe intra-abdominal, surgical site, and skin and soft tissue infections, brain abscesses, and anaerobic bacteremia [5].

The number of effective antimicrobial drugs against *B. fragilis* is relatively limited owing to its potential resistance to various classes of drugs, including β -lactams, tetracyclines, macrolides, and fluoroquinolones. Consequently, *B. fragilis* serves as a reservoir of antimicrobial resistance genes and elements [6].

Carbapenems are effective in treating *B. fragilis* infections, but the emergence of carbapenem resistance in this species is grounds for concern among clinicians [7].

In recent years, new carbapenems have been introduced, known as broad-spectrum carbapenems, which have shown good antimicrobial activity against various anaerobic and aerobic Gram-positive and Gram-negative bacteria. Therefore, broad-spectrum carbapenems are expected to play an important role in the treatment of polymicrobial infections [8]. Some of these agents, including razupenem, tomopenem, and sanfetrinem, have demonstrated significant antibacterial effects against *B. fragilis* in *in vitro* and *in vivo* experiments [9, 10, 11].

Carbapenems belong to a subgroup of β -lactam antibiotics, characterized by the presence of a ring containing an unsaturated five-membered carbon attached to nitrogen and carbon in the β -lactam ring [12]. Carbapenems inhibit bacterial cell-wall synthesis by inactivating penicillin-binding proteins. Carbapenems are stable against the action of the majority of β -lactamases [13, 14].

Over the last decade, bacterial drug efflux systems, particularly those in the resistance-nodulation-division (RND) family, have been intensively studied. The RND efflux genes in *B. fragilis* (bmeB1-16) have their own characteristics: (i) all bmeB efflux genes are transcribed, (ii) each bmeB efflux gene has a unique associated outer membrane protein (OMP) gene, and (iii) one efflux system operon (bmeABC11) contains two efflux genes (bmeB11 and bmeB11') separated by the omp gene. Similar to other Gram-negative bacteria, the *B. fragilis*

genome contains efflux systems from other classes, including ATP-binding cassette (ABC) transporters, major facilitator superfamily (MFS), and multidrug and toxic compound extrusion (MATE) pumps. Understanding the nature of the interactions between RND pumps and their interactions with pumps of other classes has important implications for the development of antimicrobial agents [15].

The development of multidrug resistance to carbapenems, metronidazole, and clindamycin in *B. fragilis* is also associated with the two aforementioned types of drug efflux pumps, RND and MATE [16]. The carbapenems most commonly used in clinical practice are imipenem, meropenem, ertapenem, and doripenem, which have demonstrated *in vitro* effectiveness against *B. fragilis* [11]. Resistance to β -lactam drugs in *B. fragilis* arises because of various molecular mechanisms, such as β -lactamase production, inhibition of β -lactam antibiotic activity through hydrolysis of the amide group in the β -lactam ring, overexpression of multidrug efflux pumps, changes in outer membrane permeability, and low affinity of its penicillin-binding proteins (PBPs) for certain β -lactams [11]. Resistance to carbapenems in *B. fragilis* isolates most commonly occurs due to the presence of the carbapenemase gene (*cfiA*), which encodes a metallo- β -lactamase (MBL). *cfiA*-positive strains typically exhibit a broad range of resistance to almost all anti-anaerobic β -lactams. In *B. fragilis*, *cfiA* is usually located near its upstream IS element, which acts as a promoter to regulate *cfiA* transcription. *cfiA*-dependent carbapenem resistance remains the dominant resistance mechanism in *B. fragilis*, despite several studies reporting potential *cfiA*-independent ones. Cordovana et al. demonstrated that *cfiA*-positive *B. fragilis* isolates consistently exhibited carbapenemase activity regardless of their minimum inhibitory concentration (MIC) for carbapenems, highlighting the importance of *cfiA* in mediating carbapenem resistance in *B. fragilis*. *cfiA* is typically found on the *B. fragilis* chromosome; however, plasmid-mediated *cfiA* has also been reported by Goto et al. The presence of the transferable plasmid-borne *cfiA* significantly increases the risk of carbapenem resistance in *B. fragilis* isolates [7].

Thus, the genomic plasticity of *B. fragilis* allows it to acquire antimicrobial resistance determinants and virulence factors through horizontal gene transfer (HGT), as well as to activate or deactivate specific resistance genes as needed [5]. Valdezate et al. (2021) investigated the genomes, taxonomy, and phylogenetic relationships of two *B. fragilis* strains (CNM20180471 and CNM20200206) that were resistant to meropenem+EDTA. Both strains carried *cfiA* genes (*cfiA*14b and a novel *cfiA*28), as well as other antimicrobial resistance mechanisms (efflux pump genes *mexAB/mexJK/mexXY-oprM*, *acrEF/mdtEF-tolC*, and *cusR*, which reduce carbapenem penetration through *OprD* repression) [5].

There is limited information regarding the mechanisms underlying carbapenem resistance in *Bacteroides* species other than *B. fragilis*. Detection of *cfiA* has not been described for these species; however, Wallace et al. found that nearly half of the non-*fragilis* *Bacteroides* species in their cohort of isolates had amplicons corresponding to the *cfiA* PCR product. This is the first report of *cfiA* detection in a non-*fragilis* *Bacteroides fragilis* group (BFG) species. However, the AM-Rfinder tool did not detect any genes annotated as *cfiA* among these strains. Additionally, none of the non-*fragilis* BFG iso-

lates harbored *cfiA*-associated IS elements detected by PCR. Furthermore, among the entire cohort of isolates studied, IHMA_8 was the only carbapenem-resistant BFSS isolate lacking detectable *cfiA*. Isolate IHMA_8 exhibited MICs of 16 and >32 g/mL for ertapenem and meropenem, respectively. Interestingly, carbapenem resistance in this strain appeared to be independent of IS activation of *cfiA* or the presence of the *cfiA* gene itself [17].

A previous study by Nagy et al. showed that BFSS isolates could be divided into two groups characterized by the mutually exclusive presence of endogenous *cepA* (Group I) or *cfiA* (Group II) [18]. However, Wallace et al. [17] demonstrated that Group II isolates represent distinct genome types due to their phylogenetic clustering. Alignment of the genomes of the Group I reference strain NCTC 9343 and Group II isolate IHMA_4, which had a closed circular genome assembled using hybrid assembly, revealed that *cepA* and *cfiA* were present in different genomic regions (Figure 1).



Figure 1 – Whole-genome alignment of BFSS Group I strain NCTC 9343 and Group II strain IHMA 4. Shown are loci containing the *cepA* and *cfiA/ccrA* genes specific to BFSS Group I and II divisions, respectively [17].

4 MODERN UNDERSTANDING OF THE ROLE OF RNAs IN BACTEROIDES SPP.

RNAs are key to the success of bacteria in occupying dynamic niches and surviving various stresses [19]. Currently, research on *Bacteroidetes* RNAs is in its infancy [20]. Unlike other gram-negative bacteria, where sRNA function is often associated with auxiliary RNA chaperones [21] or proteins containing the FinO domain [22], the global RNA-binding protein (RBP) in *Bacteroidetes* is unknown, although proteins containing the RNA recognition motif (RRM) domain have recently been proposed as candidates [23].

RNA sequencing (RNA-seq) has been applied to *Bacteroides fragilis* [24] and *Bacteroides thetaiotaomicron* [20], two model organisms used in *Bacteroides* research, revealing hundreds of non-coding RNA candidates. However, their conservation, secondary structure, and function have not yet been systematically determined. Veeranagoud et al. conducted RNA sequencing of *B. fragilis* strain 638R isolated from an abdominal abscess. Transcriptional analysis showed that 94.6% (4093 out of 4326) of the genes were transcribed in *B. fragilis* 638R, but another 40 genes that did not show transcription/expression may be transcribed at different growth stages. These data suggested that many genes with unknown functions are necessary for *B. fragilis* 638R growth [25].

Prezza et al. searched for *Bacteroides* proteins containing known RNA-binding domains using the Pfam release 32 [26].

As a result, neither Hfq homologs nor ProQ homologs were identified (Figure 2).

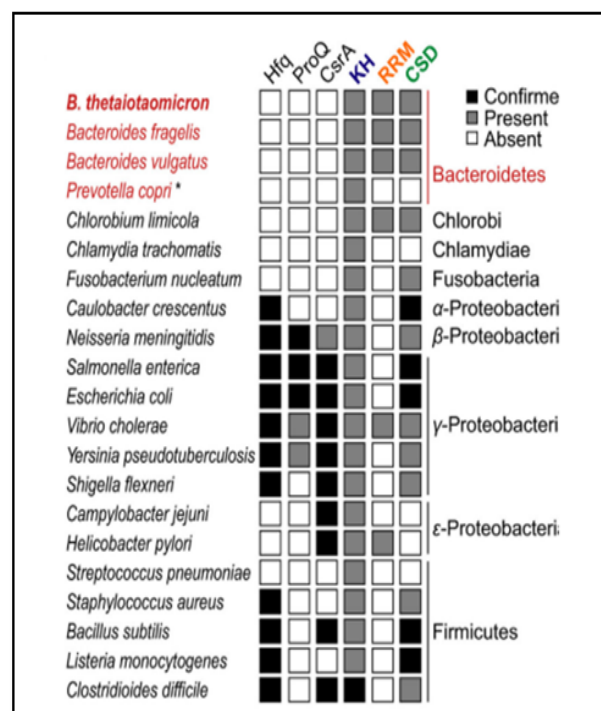


Figure 2 – Results of Pfam search for proteins containing RNA-binding domains (RBDs) in Bacteroidetes and other bacterial types. White square: not detected; gray square: detected; black square: previously established as (global) RNA binder. CSD, cold shock domain; KH, KH homology; RRM, RNA recognition motif. Asterisk: For *Prevotella copri*, there is currently no complete genome available, so the hits do not guarantee their completeness [26].

Similarly, it has been found that CsrA/RsmA, as well as the highly conserved translational regulator RBP [27], are also absent in Bacteroidetes. Instead, RNA recognition motif (RRM) domains, cold-shock domains (CSD), and occasionally observed KH motifs, which are also found in other bacterial RBPs, have been identified. While it is established that three RRM-1 and CSP proteins may act as regulatory RBPs in *Bacteroides*, it has also been speculated that proteins containing KH motifs in *Bacteroides thetaiotaomicron* do not possess RNA chaperone functions [4].

The KH, RRM-1, and CSD domains consist of approximately 70 amino acids each and can bind to single-stranded regions of nucleic acids [28]. Type II KH domains, which are predominant in prokaryotes, consist of three β -strands, two of which are oriented parallelly [29]. KH domains are found in PNPase and ribosomal protein S3, where they mediate RNA binding, and in transcription elongation proteins, where they initiate binding to chromosomal DNA.

RRM domains consist of four antiparallel β -strands and two α -helices. CSD has a β -barrel structure, and the binding of CSP remodels the folding of its RNA ligands [30].

The absence of Hfq, ProQ, and CsrA homologs, but the presence of proteins containing RRM-1 and CSD domains in Bacteroidetes, may indicate an RNA biology that is fundamentally different from the RNA biology of Proteobacteria, which has served as a bacterial model for RNA biology for

Table 1 – Functional groups of genes affected by SI antibiotics [36].

Functional groups of genes affected by SI antibiotics			
Antibiotic	Organism	Effect	References
Tetracyclines	<i>Bacteroides spp.</i>	Enhanced gene transfer (conjugation of antibiotic resistance genes)	[37]
	<i>S. epidermidis</i>	Stimulation of bacterial adhesion	[38]
	<i>Streptococcus sp</i>	Changes in exoprotein secretion	[39]
b-lactams	<i>Staphylococcus sp</i>	Decreased biofilm formation	[40]
Cerulenin	<i>S. aureus</i>	Inhibition of protein secretion	[41]
Aminoglycoside	<i>P. aeruginosa</i>	Increased biofilm formation	[42]
	<i>S. pneumoniae</i>	Increased mutation frequency	[43]
Fluoroquinolones	<i>E. coli</i>	Reduced hemolytic activity. Induction of colicin synthesis	[44]
	<i>S. aureus</i>	Increased adhesion	[45]
	<i>S. pneumoniae</i>	Increased mutation frequency	[43]
	<i>Mycobacterium fortuitum</i>	Increased mutation frequency	[46]
Macrolides	<i>Mycobacterium avium</i>	Decreased biofilm formation	[47]
	<i>P. aeruginosa</i>	Inhibition of quorum sensing (virulence suppression)	[48]
Lincosamides	<i>Bacteroides fragilis</i>	Altered cell morphology and increased DNA fragmentation	[49]
	<i>S. aureus</i>	Changes in exoprotein expression	[39]
Oxazolidinone	<i>S. aureus</i>	Decreased secretion of virulence factors	[50]
Mupirocin	<i>P. aeruginosa</i>	Reduced biofilm formation . Reduced flagellin expression	[51]

decades. This, in turn, suggests that many new RNA-related mechanisms and functions await discovery and should contribute to future investigations of RBPs in *Bacteroides* [4].

Whole-genome RNA-sequencing identified 124 intergenic sRNAs in *B. thetaiotaomicron* [31]. The *B. thetaiotaomicron* genome possesses some unique characteristics compared to other bacterial RNA models, as they are rich in AT content (GC content of 42%) and lack known RBPs such as FinO-like proteins [4].

Prezza et al. found that the absence of classical RNA chaperones and low GC content in *Bacteroides* did not affect the general properties of their sRNAs [4].

Currently, only two trans-encoded sRNAs have been characterized in *Bacteroides*: RteR [32] and GibS [20]. GibS and RteR belong to a cluster of 12 partially conserved sRNAs present in most *Bacteroides* species but do not extend beyond the genus level [4].

Another feature of *Bacteroides* RNA biology is the absence of the classical sigma factor ($\sigma 70$) encoded by the proteobacterial rpoD gene. Instead, members of this type harbor an unusual RpoD-like primary transcription factor, σ ABfr, as well as an arsenal of alternative extracytoplasmic function sigma factors (ECFs) [20].

5 TRANSCRIPTOMIC ANALYSIS OF THE ADAPTIVE RESPONSE OF *BACTEROIDES* SPP. TO LOW DOSES OF ANTIMICROBIAL DRUGS

The resident microbiota is influenced by sub-inhibitory concentrations (SIC) of antimicrobial drugs, which can lead to changes in the interactions between pathogenic and host-as-

sociated bacteria, related to the pleiotropic regulation of bacterial gene expression as an adaptive response [33]. In *in vitro* studies, cellular changes related to morphology, physiology, and protein expression of anaerobic bacteria have been reported within the SIC framework of antimicrobial drugs [34]. Moreover, SIC of antimicrobial drugs result in persistent changes in the gene expression patterns of *B. fragilis* [35]. Considering this adaptive response to the SIC of antimicrobial drugs, studying the expression of the bacterial genome will lead to a better understanding of the microbial mechanisms for overcoming antimicrobial chemotherapy [35].

As mentioned above, it has long been known that antibiotics at low concentrations exert multiple effects on bacterial cells. However, it was only with the advent of genome transcription analysis that these actions were extensively studied at the cellular metabolism level. All antibiotics, regardless of their receptors and mode of action, exhibit the phenomenon of hormesis and induce significant transcriptional activation at low concentrations. Table 1 presents the results of the studies that used microarray, proteomic, and promoter-reporter fusion library technologies to elucidate the ability of sub-inhibitory concentrations (SI) of antibiotics to induce global changes in gene transcription [36].

Unlike physiological reactions, the effect of low doses of antibiotics is relatively uniform and leads to the enhanced transfer of antibiotic resistance genes, often conferring resistance to structurally unrelated antibiotics. Studies conducted by Davies et al. have shown that bacterial transcriptional responses to sub-inhibitory antibiotics, assessed using these technologies, are not constant and depend on multiple factors

such as experimental conditions, nature and concentration of the antibiotic used, bacterial taxonomy, and genotype. It has been established that the extent of transcriptional response does not necessarily imply automatic conversion to the corresponding phenotype [36].

6 MASS SPECTROMETRY AND PROTEOMICS

Microorganisms have been at the forefront of proteomics. Modern proteomic studies have covered the expression, secretion, activation, degradation, and various protein modifications. Proteomics-based mass spectrometry enables the identification and quantitative analysis of complex protein mixtures that constitute proteomes. Proteomic profiling methods are predominantly based on liquid chromatography combined with tandem mass spectrometry (LC-MS/MS). Most systems-level studies on *Bacteroides* species have focused on the genomics of the pathogen. Genomic data do not always provide information regarding bacterial environmental plasticity and the nature of antibiotic resistance. Proteomics, in turn, seeks to provide information on the dynamic regulation of bacteria in changing environmental conditions, allowing a detailed comparison of proteomes, including protein interactions, modifications, and cell localization. However, a limited number of studies exist that describe the proteomics characteristics of the *B. fragilis* group.

Its pathogenicity has been attributed to various virulence traits. One is its ability to tolerate high concentrations of bile salts in the gastrointestinal tract (GIT). Bile salts, which act as detergents, can cause membrane permeabilization and cell death. Modulation of outer membrane proteins (OMPs) is considered a critical mechanism for bile salt resistance. In a study by Boente et al. (2016), the identification of *B. fragilis* proteins associated with the stress induced by high concentrations of bile salts was carried out [53]. The outer membrane of *B. fragilis* strain 638R was isolated after growth in the presence or absence of 2% conjugated bile salts. The resulting membrane fractions were separated using SDS-PAGE and subjected to electrospray ionization quadrupole time-of-flight tandem mass spectrometry (ESI-Q/TOF). Through this approach, 37 proteins were identified, with nine exclusively expressed in the absence of bile salts and eight proteins expressed solely in the presence of bile salts. These differentially expressed proteins are involved in essential cellular functions such as membrane transport, nutrient uptake, and protein-protein interactions. This study highlights the dynamic alteration of OMP composition in *B. fragilis* during its resistance to bile salt-induced stress, enabling its adaptation to environmental changes. Moreover, proteomic analysis of OMPs provides valuable insights into potential targets for functional analysis. Understanding the mechanisms underlying bile salt resistance in *B. fragilis* will contribute to our knowledge of its pathogenicity and aid in the development of targeted therapeutic strategies.

The human gut harbors a complex network of microbial interactions that remain poorly understood. In particular, the interplay between *Bacteroides* and *Bifidobacterium*, two prominent genera in the intestinal microbiota, has gained attention because of its potential impact on their survival and function. In a study by Rios-Covián et al. (2016), co-cultures of *Bifidobacterium longum* NB667 and *B. fragilis* DSMZ2151

were used to investigate the underlying mechanisms governing their interactions [54]. To elucidate the dynamics of this co-culture, proteomic analysis was employed using two-dimensional difference gel electrophoresis (2D-DIGE) and bacterial metabolites were quantified using chromatographic techniques. Co-culture conditions influenced the growth patterns of *B. longum* and *B. fragilis*, accompanied by alterations in the production of specific proteins and metabolites. Notably, the combined culture stimulated the upregulation of pyruvate kinase in *B. longum*, a key enzyme involved in carbohydrate catabolism, and downregulated phosphoenolpyruvate carboxykinase in *B. fragilis*. These findings suggest a shift in carbohydrate utilization strategies between the two species. Additionally, the FKBP-type peptidyl-prolyl cis/trans isomerase, a protein with chaperone-like activity, was overexpressed in *B. fragilis* during co-culture, indicating the induction of a stress response in this bacterium. These results provide valuable mechanistic insights into the complex interplay between the *Bacteroides* and *Bifidobacterium* populations within the intestinal environment. The combined application of proteomic and metabolomic approaches has contributed to our understanding of the molecular mechanisms underlying these interactions.

B. fragilis is often involved in polymicrobial infections, and piperacillin/tazobactam (PTZ) is frequently prescribed. However, sub-inhibitory concentrations of antibiotics encountered during therapy can induce phenotypic changes in bacteria. In a study by Veloso et al. (2013), alterations in the proteomic profile of *B. fragilis* grown in a sub-minimum inhibitory concentration (sub-MIC) of PTZ were investigated using 2-D electrophoresis coupled with matrix-assisted laser desorption/ionization TOF/TOF [55]. Analysis of the 2-D gels revealed 18 spots with significantly different volume percentages between experimental conditions, of which 12 were successfully identified using tandem mass spectrometry (MS/MS). Among the proteins that exhibited decreased abundance under sub-MIC conditions, two were involved in glycolysis (glyceraldehyde-3-phosphate dehydrogenase and triose phosphate isomerase), two were associated with amino acid metabolism (oxoacyl-(acyl-carrier protein) synthase II and dihydrodipicolinate reductase), and one was linked to fatty acid metabolism (UDP-N-acetylglucosamine acyltransferase). Conversely, among the proteins with increased abundance, three ATP synthases (alpha, beta, and alpha type V), potentially associated with antibiotic resistance via efflux pumps, were identified, along with one protein involved in glycolysis (enolase) and one involved in protein degradation (aminoacyl-histidine dipeptidase). In summary, these findings demonstrate significant proteomic changes in *B. fragilis* induced by sub-inhibitory concentrations of PTZ [55].

7 MASS SPECTROMETRY AND ANTIBIOTIC RESISTANCE

Almost all clinically relevant microorganisms exhibit antibiotic resistance and antibiotic resistance of *Bacteroides* spp. is an emerging threat to public health. *Bacteroides* exhibit different patterns of antibiotic resistance, which can affect their susceptibility to various antimicrobial agents. Understanding these differences is crucial for the effective treatment of *Bacteroides*-related infections. Some *Bacteroides* species such

as *B. faecis* and *B. thetaiotaomicron* have very similar 16S rRNA sequences and ribosomal proteomic patterns. Therefore, distinguishing between the species may be difficult. Currently, several antibacterial agents are highly effective against *Bacteroides*. One of the most common is metronidazole, which is prescribed for the majority of infections caused by anaerobic bacteria. It has been reported by the Food and Drug Administration (FDA) that metronidazole is effective against the *Bacteroides fragilis* group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus*) infections resistant to clindamycin, chloramphenicol, and penicillin. Combined resistance to metronidazole and other antibiotics leads to untreatable forms of infection (e.g., intra-abdominal infections, skin infections, gynecological infections, bacterial septicemia, bone and joint infections, central nervous system infections, lower respiratory tract infections, and possibly endocarditis). Therefore, a better understanding of adaptation mechanisms and potential consequences in the context of antibiotic therapy is needed.

Carbapenemases are associated with carbapenem resistance. Surveillance of *cfiA*-positive *B. fragilis* is crucial to monitor its prevalence in clinical settings. As indicated above, *B. fragilis* can be classified into two categories based on the presence or absence of *cfiA*. *cfiA*-positive isolates belonged to division II, whereas division I *B. fragilis* was *cfiA*-negative. Division II isolates carry a silent *cfiA* gene that can be overexpressed through insertion of a mobile genetic element, leading to phenotypic resistance to carbapenems. In a study by Jeverica et al. (2019), the prevalence of division II *B. fragilis* isolates among bloodstream and non-bloodstream specimens was determined in two major Slovenian tertiary care hospitals and their impact on imipenem resistance was assessed [56]. *B. fragilis* isolates obtained from blood and non-blood samples between 2015 and 2017 were included in this study. The obtained mass spectra were analyzed using a taxonomy library and further examined using a *cfiA* library to differentiate between division I and II isolates based on score values. The minimum inhibitory concentration (MIC) of imipenem was determined. A total of 623 *B. fragilis* isolates were analyzed, of which 47 (7.5%) were obtained from bloodstream samples and 576 (92.5%) from non-bloodstream samples. Among the isolates, 51 (8.2%) were classified as division II (*cfiA*-positive). This study highlights the prevalence of division II carbapenem-resistant *B. fragilis* isolates in Slovenian tertiary care hospitals, with a high proportion observed in bloodstream samples. Additionally, all the imipenem-resistant isolates belonged to division II, suggesting an association between division II status and imipenem resistance. These findings emphasize the importance of surveillance and monitoring carbapenem resistance in *B. fragilis*, particularly in bloodstream infections.

A similar study by Kawamoto et al. (2021) aimed to evaluate the ability of a new MALDI-based subtyping module integrated into the MALDI-TOF MS system to detect *cfiA*-positive strains of *B. fragilis* [57]. In total, 396 *B. fragilis* strains isolated between 2006 and 2019 were included in the analysis. This technology was used to identify presumptive *cfiA*-positive strains, which were confirmed using PCR. Additional examinations were conducted on *cfiA*-positive *B. fragilis*, including the analysis of insertion sequence (IS) elements

and assays to assess meropenem hydrolysis activity. Of the 396 strains, the subtyping module detected 33 presumptive *cfiA*-positive strains (8.3%) and subsequent PCR confirmed the presence of *cfiA* in 32 strains. The sensitivity and specificity of this subtyping method for detecting *cfiA*-positive *B. fragilis* were determined to be 100.0% and 99.7%, respectively. Among the 32 *cfiA*-positive strains, seven possessed IS elements known to induce high *cfiA* expression. Notably, all seven strains exhibiting both *cfiA* and IS showed hydrolytic activity and resistance to meropenem and imipenem. In conclusion, the tested subtyping technology demonstrated rapid and accurate detection of *cfiA*-positive *B. fragilis* strains, making it a valuable tool for surveillance in clinical settings. This technology provides reliable support for monitoring and managing *cfiA*-positive *B. fragilis* strains, aiding in the prevention and control of carbapenem resistance.

Unfortunately, routine susceptibility testing of anaerobic bacteria in clinical practice is not common [58]. Therefore, periodic monitoring of susceptibility patterns is essential. In a study by Treviño et al. (2012), an updated assessment of resistance in the *B. fragilis* group was provided, with a focus on carbapenem resistance and the detection of metallo-beta-lactamase (MBL)-producing strains, while comparing the two molecular typing methods [59]. A total of 830 non-duplicate clinical isolates from the *B. fragilis* group collected between 2006 and 2010 were analyzed. *B. fragilis* was the most prevalent species (59.5%). The overall susceptibility rates of the *B. fragilis* isolates were as follows: penicillin (13.3%); amoxicillin/clavulanic acid (89.6%) piperacillin/tazobactam, (91.8%); cefoxitin (65.8%) ertapenem, (95.9%) imipenem, (98.2%) clindamycin, (53.4%); and metronidazole (96.4%). The sensitivity rates to amoxicillin/clavulanic acid, cefoxitin, clindamycin, and metronidazole did not change significantly over time. However, a slight increase in the resistance to ertapenem and imipenem was observed. Imipenem resistance and carbapenemase production were first detected in a laboratory in 2007, which marked the first report of carbapenemase-producing *B. fragilis* in Spain. Among the imipenem-resistant isolates, six were confirmed to be MBL-producing and all were positive for *cfiA*. Four isolates were positive for IS-like elements upstream of *cfiA*, whereas two were negative. Automated repetitive sequence-based (rep-PCR) and MALDI-TOF MS revealed extensive genetic diversity among the carbapenem-producing strains, suggesting the acquisition of novel resistance genes rather than clonal dissemination. Both methods have demonstrated utility for the rapid and accurate identification and strain typing of *B. fragilis* in routine laboratory practices. Considering the increasing number of *Bacteroides* spp. isolated from blood cultures and the emergence of carbapenemase-producing strains, antimicrobial susceptibility testing is strongly recommended, at least in critically ill patients, to guide appropriate antimicrobial treatment decisions.

8 CONCLUSIONS

Multi-omics studies of *Bacteroides* have made significant contributions to the understanding of the biology and mechanisms of action for these bacteria. These findings expand our knowledge of the transcriptional and proteomic responses of *Bacteroides* to various factors, including sub-inhibitory concentrations of antibiotics. Overall, multiomics studies

of *Bacteroides* serve as important tools for investigating and understanding the microbial mechanisms of antimicrobial chemotherapy resistance and developing new approaches to combat infections.

AUTHOR CONTRIBUTIONS

Conceptualization, S. K. and P. T.; formal analysis, E. Z.; resources, E. Z.; writing-original draft preparation, E. Z, S. K., P. T., and D. B.; and writing-review and editing, E. Z. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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BACTEROIDES ТОБЫНДАҒЫ БАКТЕРИЯЛАРДЫ МУЛЬТИОМИЯЛЫҚ ЗЕРТТЕУДІҢ ЗАМАНАУИ ПЕРСПЕКТИВАЛАРЫ

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ТҮЙІН

Бұл шолу *Bacteroides* spp. тобына жататын бактерияларды зерттеуге арналған мульти-омикалық (геномдық, транскриптомдық және протеомдық) тәсілдерді қарастырады. Аталған бактериялар – адам ішегіндегі ең көп таралған анаэробтар ретінде танылып, іш-құрсақты анаэробты инфекциялардың жартысынан астамын тудырады. Мульти-омикалық тәсілдер *Bacteroides* геномынан вируленттілік факторларын, антимикробтық төзімділік гендерін және басқа да функционалдық элементтерді анықтауға мүмкіндік берді. Бұл ақпарат аталмыш бактериялардың патогендік потенциалын және анаэробты инфекциялардың дамуына қатысын түсіну үшін өте маңызды. Шолуда *Bacteroides* бактерияларының антимикробтық препараттардың субингибиторлық концентрацияларына ұшырағаннан кейінгі транскрипциялық жауабы, сондай-ақ протеомдық талдау әдістері мен *Bacteroides* протеомын зерттеудегі жетістіктері қарастырылды. Жалпы алғанда, *Bacteroides* бактерияларын мульти-омикалық зерттеудің қазіргі заманғы бағыттары олардың биологиясын, функционалдық сипаттамаларын және ішек экожүйесіндегі экологиялық рөлін тереңірек түсіну үшін әртүрлі омикалық тәсілдерді біріктіру мүмкіндігін көрсетеді.

Кілт сөздер: геномика, транскриптомика, протеомика, субингибиторлық концентрациялар, карбапенемдер, бактероидтар.

СОВРЕМЕННЫЕ ПЕРСПЕКТИВЫ МУЛЬТИОМНЫХ ИССЛЕДОВАНИЙ БАКТЕРИЙ ИЗ ГРУППЫ BACTEROIDES

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АБСТРАКТ

В этом обзоре рассматриваются мультиомные (геномные, транскриптомные и протеомные) подходы к изучению бактерий группы *Bacteroides* spp., которые являются наиболее распространенными анаэробами в толстой кишке человека и ответственны за более чем половину всех внутрибрюшных анаэробных инфекций. Эти многомерные подходы позволили идентифицировать факторы вирулентности, гены устойчивости к противомикробным препаратам и другие функциональные элементы генома *Bacteroides*. Эта информация имеет решающее значение для понимания патогенного потенциала этих бактерий и их роли в развитии анаэробных инфекций. В этом обзоре рассматривается транскрипционный ответ *Bacteroides* после воздействия субингибирующих концентраций антимикробных препаратов, а также основные методы протеомного анализа и достижения в изучении протеома *Bacteroides*. В целом, современные перспективы мультиомических исследований *Bacteroides* подчеркивают возможность интеграции различных омических подходов для более полного понимания их биологии, функциональных характеристик и экологической роли в экосистеме кишечника.

Ключевые слова: геномика, транскриптомика, протеомика, субингибиторные концентрации, карбапенемы, бактероиды.