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THE *BACTEROIDES FRAGILIS* TOXIN (*BFT*) GENE: ITS ROLE IN VIRULENCE, REGULATION, AND DISEASE

***A. Bekbayeva [1,2], B.S. Kongyr[3], E.V. Zholdybayeva[1], S.S. Kozhakhmetova[1]**

[1]*National Center for Biotechnology, 13/5, Kurgalzhynskoye road, Astana,Kazakhstan, 010000;*
[2]*L.N. Gumilyov Eurasian National University, 2 Satbaev st., Astana, Kazakhstan, 010000;*
[3]*Al-Farabi Kazakh National University, 71 Al-Farabi Ave., Almaty, Kazakhstan, 050040;*
** bekbayeva@biocenter.kz*

ABSTRACT

Bacteroides fragilis can be divided into two different groups of strains: an *enterotoxigenic strain (ETBF*) that has a pathogenicity island and the Bacteroides fragilis toxin gene (*bft*) and a *non-toxigenic strain (NTBF*) that does not have a pathogenicity island and the *bft* gene. Recent studies have shown that there is a correlation between the presence of the *bft* gene in enterotoxigenic Bacteroides fragilis (ETBF) strains and various gastrointestinal disorders, including colorectal cancer and inflammatory bowel disease. Due to its ability to disrupt the intestinal epithelial barrier, promote chronic inflammation, and affect carcinogenesis, the presence and expression of *bft* significantly contribute to the pathogenicity of ETBF. This review provides an analysis of the genetic structure, allelic variants, and regulatory mechanisms of *bft*. A membrane protein vital to cell adhesion, E-cadherin, is disrupted by *Bacteroides fragilis* toxin, resulting in disruption of epithelial integrity and facilitating bacterial entry. BFT also stimulates important intracellular signaling pathways, including mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light chain enhancer of activated B cells (NF-kB). These signaling pathways significantly influence both cellular transformation and inflammatory responses. This review also highlights advances in diagnostic methods and innovative therapeutic approaches, such as the development of allosteric inhibitors that can block BFT activity. Although much has been learned about the regulation and function of the *bft* gene, there are significant gaps in understanding the environmental factors that lead to gene upregulation and its molecular interactions. Future research should aim to elucidate these mechanisms to facilitate the development of targeted therapies.

Keywords: *Bacteroides fragilis* toxin (*bft*); enterotoxigenic *Bacteroides fragilis* (ETBF); epithelial barrier disruption; MAPK pathway; NF-kB pathway; colorectal cancer; allosteric inhibitors; therapeutic strategies.

1. INTRODUCTION

In recent years, there has been an increased interest in non-spore-forming anaerobic bacteria worldwide, including in European research centers, with attempts to study their role in both the etiology of human infections and in the physiological microflora of the intestine. Among these bacteria, a special place is occupied by *Bacteroides fragilis,* a leading non-spore-forming anaerobe that plays a key role as an infectious agent [1]. *Bacteroides fragilis,* a prominent member of the normal colonic microflora, is a significant and often isolated anaerobic bacterium in clinical laboratories, associated with both mono- and polymicrobial illnesses with other aerobic and facultative anaerobic bacteria. *B. fragilis* represents around 5% of gastrointestinal microflora, however it is regarded as the most prevalent species within the *Bacteroides* genus, exhibiting infection rates of 60–80% [2, 3]. It is a Gram-negative, anaerobic yet moderately aerotolerant bacterium present in nearly all individuals. *B. fragilis* ferments dietary fibre and resistant starches and can metabolise various carbohydrates, including host glycans [4]. The majority of *B. fragilis* are commensal organisms. Certain strains of *B. fragilis* exhibit virulence, designated as *enterotoxigenic B. fragilis* (ETBF), which cause secretory diarrhoea and damage to colonic epithelium by the production of a proteolytic toxin known as *B. fragilis* toxin *(*BFT) [5]. Studies have shown that enterotoxigenic *B. fragilis* (ETBF) strains possess enhanced pathogenicity relative to *non-toxigenic* (NTBF) strains and are associated with several conditions, including septicaemia, diarrhoea, irritable bowel syndrome (IBS), and colorectal cancer (CRC) [6].

BFT prompts the cleavage of E-cadherin and the reorganisation of actin, resulting in alterations in cell morphology and the attainment of metastatic potential. The activation of the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-kB) and Mitogen-Activated Protein Kinase (MAPK) pathways, triggered by BFT, enhances cytokine release and facilitates the infiltration of immunosuppressive cells into the colonised niche. ETBF or BFT augments cancer cell stemness in colorectal and breast cancers. Nonetheless, the fundamental mechanisms and the existence of cellular receptors for BFT that facilitate downstream signalling remain ambiguous [5].

Three different variations of the *bft* gene have been identified: *bft-1*, *bft-2*, and *bft-3*, each differing in geographic distribution and potential pathogenicity. Despite extensive studies, the molecular mechanism underlying fragilisin function, control of *bft* expression and the specific role of ETBF in human diseases require further study [7].

The aim of this review is to comprehensively analyze the bft gene, referring to the available data including its genomic structure, pathogenicity function, and regulatory mechanisms. Additionally, we will examine its clinical significance and potential as a target for diagnostic and therapeutic approaches. This paper aims to synthesise existing research on the *bft* gene, emphasising its significance in the virulence of *B. fragilis* and the ongoing difficulty in comprehensively understanding its impact on human health and disease.

2. STRUCTURE AND VARIANTS OF THE *BFT* GENE

The *bft* gene of *Bacteroides fragilis* encodes *Bacteroides*

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fragilis toxin (BFT), a zinc-dependent metalloprotease implicated in a variety of gastrointestinal diseases. This gene is located on a 6-kb transposable element known as the *B. fragilis* pathogenicity island (BFPAI), which is bordered by genomic regions encoding mobilization proteins and is involved in the regulation of *bft* expression. Based on the presence of BFPAI and adjacent regions, three main groups of *B. fragilis* strains have been defined. The first group includes ETBF strains containing both BFPAI and adjacent regions (pattern I). The second category is represented by nontoxigenic strains (NTBF), which contain neither BFPAI nor adjacent regions (pattern II). The third group consists of NTBF strains that have adjacent regions but lack BFPAI itself (pattern III). Three allelic variants have been identified for the *bft* gene: *bft*-1, *bft*-2, and *bft*-3, encoding different toxin isoforms designated BFT-1, BFT-2, and BFT-3, respectively. Results from clinical specimens vary with respect to the prevalence of these isoforms, with *bft*-1 and *bft*-2 being the most common [8, 9]. ETBF strains may contain two copies of the same *bft* genotype, but mixed *bft* alleles have not been reported in a single ETBF strain to date. The *bft* genes are located on chromosomes with a G+C content of 39% and are predicted to encode a holotoxin consisting of 397 amino acid residues with an expected molecular weight of approximately 44.5 kDa. The structure of BFT is proposed to be a preproprotein holotoxin. The functional domain of the mature toxin for each *bft* allele contains an extended zinc-binding metalloprotease motif HEXXHXXGXXH and a nearby methionine residue precisely aligned with this motif. These data place BFT in the matrix metalloproteinase (matrixin) subfamily of the metzincin superfamily of zinc-dependent metalloproteases. Limited homology between eukaryotic matrix metalloproteases and BFT suggests that BFT may be an ancestral form [10, 11]. The proteolytic activity of BFT is essential for its biological function, with each toxin molecule containing one gram-atom of Zn^{2+} [12, 13].

The *bft* gene comprises several regions, including a signal peptide that ensures secretion, a prodomain that maintains the toxin in an inactive form, and a catalytic domain responsible for proteolytic activity. The pre-protein consists of 397 amino acid residues, of which 18 residues form the signal peptide, 193 form the prodomain, and 186 form the catalytic domain. BFT is activated by cleavage of the prodomain, which leads to the release of the active catalytic domain [7]. All three *bft* alleles have a high degree of sequential similarity, but differ in certain regions, which causes differences in the amino acid sequences of the toxins they encode. These differences may affect biological activity and toxicity. BFT-2 demonstrated higher specific activity and pronounced biological effects both in vitro and in vivo compared to BFT-1 and BFT-3 [14, 15].

The geographic distribution of *bft* alleles varies among clinical isolates. The most common variant among B. fragilis isolates from humans is *bft*-1. The *bft*-2 allele is considered the most virulent, capable of causing tissue damage, while *bft*-3 is predominantly distributed in Southeast Asia [7, 9]. However, the global distribution of *bft* alleles remains difficult to assess due to limited data. According to the available information in the National Center for Biotechnology Information (NCBI) Home - Nucleotide (NCBI) database, a total of 137 *bft* gene sequences were uploaded between 1997 and 2024. The most abundant allele is *bft1*, which occurs in 69 of 137 cases; *bft2* is found in only eight sequences, and *bft3* is the rarest, with only three sequences identified. The remaining 57 sequences were classified as undetermined by *bft* allele type. Of the eight *bft2* sequences, six were isolated in the United States - one in Arizona and one in Boston. One sequence was obtained in Denmark, and another, identified in 2012, does not contain an indication of geographic origin. All three *bft3* sequences were also isolated in New York. It is important to note that the NCBI database does not contain information on the geographic origin of *bft* isolates before 2014. In addition, in Kazakhstan in 2020, the *bft1* allele was identified, the sequence of which was sent to NCBI by the National Center for Biotechnology. This information is illustrated in the diagram presented in Figure 1 [16].

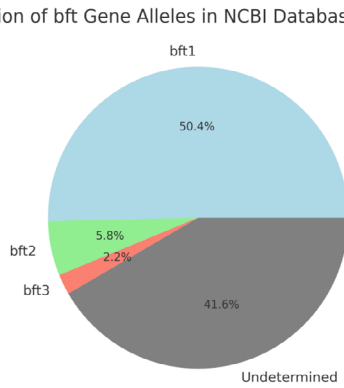

Figure 1. Distribution of *BFT* gene alleles in the NCBI database (1997-2024).

All *BFT* isoforms act via a common mechanism, with their main target being the extracellular domain of E-cadherin on the surface of epithelial cells, which leads to disruption of intercellular adhesion and increased permeability of the intestinal barrier. However, differences between isoforms may result in variations in their efficacy and the degree of immune response elicited in the host. Recent studies have highlighted the C-terminal region of *BFT* as key to its biological activity, suggesting that variations in this part of the molecule among different isoforms may explain differences in their action [17].

3. ROLE OF THE *BFT* GENE IN VIRULENCE

The *bft* gene of Bacteroides fragilis encodes a metalloprotease toxin known as fragilysin, which is a key virulence factor for this bacterium. Below is an overview of its main functions and effects:

3.1 Molecular mechanism of action of BFT protein on intestinal epithelium

Fragilisin (BFT) is a metalloprotease toxin with a molecular weight of about 20 kDa, which is thermolabile and zinc-dependent. Fragilisin was found to induce tumor processes by cleaving the extracellular domain of E-cadherin. Its mechanism of action begins with the binding of the toxin to receptors on the surface of epithelial cells, which triggers an intracellular signaling cascade. As a result, proteolytic cleavage of the extracellular domain of E-cadherin occurs, leading

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to disruption of the integrity of the epithelial barrier and an increase in its permeability. The proteolytic activity of BFT is a key link in the implementation of these effects [12, 18].

The intestinal epithelial barrier separates the intestinal luminal bacteria and their components, which are perceived as the external environment, from the sterile internal tissues of the body. This separation is ensured, in part, by cell-cell contacts, including tight junctions (TJs), which play a key role in maintaining barrier impermeability and preventing translocation of both commensal and pathogenic microorganisms. The integrity and functionality of the epithelial barrier depend on intercellular junctional complexes located in the apical portion of cells and include tight junctions (TJs), adherens junctions (AJs), and desmosomes, all of which interact with the cytoskeleton. The TJ complex includes three groups of transmembrane proteins: proteins of the claudin family, proteins with the MARVEL domain (including occludin, tricellulin, and MarvelD3), and proteins of the immunoglobulin superfamily, such as junctional adhesion molecules (JAMs) and the coxsackievirus and adenovirus receptor (CAR). The cytoplasmic plate of tight junctions is formed by scaffold proteins such as zonula occludens (ZO-1, ZO-2, ZO-3), cingulin, cingulin-like proteins, and afadin, which anchor the transmembrane structure to cytoskeletal elements. In addition, tight junctions interact with many other proteins involved in signal transduction and membrane trafficking [19].

BFT is able to disrupt the structure of the intestinal epithelial zonula adherens tight junctions by cleaving E-cadherin, which leads to: (a) delocalization of other tight junction components, (b) loss of cell adhesion, (c) reorganization of the actin cytoskeleton, (d) translocation of β-catenin to the nucleus, (e) secretion of proinflammatory signaling molecules, and (f) fluid loss. Together, these processes contribute to the development of diarrhea and related pathologies. Thus, ETBF carriers have an increased risk of developing inflammatory bowel disease and colorectal cancer. BFT expression is associated with early stages of carcinogenesis and has been shown to activate NF-kB and β-catenin/Tcf signaling cascades, leading to increased expression of the c-Myc oncogene and the proinflammatory cytokine interleukin-8 (IL-8), factors closely associated with colorectal cancer progression [20].

3.2 The role of the bft gene in the pathogenicity of B. fragilis strains

Recent studies have further confirmed the correlation between enterotoxigenic Bacteroides fragilis (ETBF) strains and colorectal cancer development. ETBF strains were found to be significantly more frequent in samples from patients with colorectal cancer compared to healthy individuals. Moreover, the frequency of *bft* gene detection correlated with the presence and severity of colorectal lesions belonging to the neoplastic spectrum, indicating a possible role of the toxin in the early stages of carcinogenesis [21]. Enterotoxigenic B. fragilis has been characterized as an important initiator and promoter of human colorectal cancer. The signaling cascades activated by BFT in colonic epithelial cells are highly complex, and some of them remain poorly understood. Zinc-dependent metalloprotease toxin binds to a receptor on the surface of epithelial cells and interacts with E-cadherin, a transmembrane protein that plays a key role in maintaining intercellular adhesion. Proteolytic cleavage of E-cadherin results in separation of its extracellular ectodomain (weight approximately 80 kDa), after which the remaining intracellular fragment undergoes additional processing involving presenilin-1/γ-secretase. These processes disrupt intercellular contacts, activate the nuclear signaling molecule β-catenin, and stimulate expression of the proto-oncogene c-myc, promoting cell proliferation and potential malignant transformations. In addition, BFT activates NF-kB (nuclear factor kappa-light chain of activated B cells) and MAPK (mitogen-activated protein kinase) signaling pathways, leading to the secretion of interleukin-8 (IL-8) and tumor necrosis factor α (TNFα). IL-8 is considered a key mediator of tumor cell proliferation, angiogenesis, and growth [22].

3.3 *Cooperative Functions with Additional Virulence Factors*

The pathophysiology of colorectal cancer may also be influenced by other virulence factors that *B. fragilis* produces, including as the metalloprotease fragilysin and the polysaccharide capsule, in addition to the BFT toxin. For example, the polysaccharide capsule has been linked to immune evasion and the stimulation of inflammatory responses, both of which can provide an environment that is conducive to tumor growth [23]. Although fragilysin is a crucial virulence factor, other components of the *B. fragilis* pathogenicity island may enhance its activity. These elements and fragilysin working together can improve the bacterium's capacity to penetrate, colonize, and spread illness [24].

4. REGULATION OF THE *BFT* GENE

According to research, certain regulatory systems inside *B. fragilis* control the expression of the *bft* gene. For example, research has found regulatory components that affect *bft* transcription, although the specific mechanisms are still being studied. In their paper, Franco et al. investigate how the *Bacteroides fragilis* toxin gene (*bft*), which codes for BFT, a zinc-dependent metalloprotease with virulence characteristics, is expressed. It was found that maximum *BFT* expression and production of active BFT require not only the pathogenic BfPAI island itself, but also adjacent DNA regions. The regulatory region of approximately 700 base pairs located upstream of *bft* contains promoter sequences that are critical for transcription. It was discovered that these areas help ensure the toxin's optimum biological activity by properly digesting and secreting it. Their protective function is demonstrated by the fact that *bft* expression can be harmful to *Bacteroides fragilis* cells when these regulatory components are absent [25].

The *bft* gene encodes the BFT toxin, which is produced as an inactive precursor (propeptide). Proteolytic processing is essential for the activation of the enzyme. Research indicates that the bacterial protease fragipain (Fpn), synthesized by *B. fragilis*, cleaves the anti-inhibitory prodomain of BFT, hence activating the toxin. The lack of Fpn leads to reduced virulence of *B. fragilis*, underscoring the significance of this protease in pathogenesis [26].

4.1 Role of Environmental Factors in bft Expression

Environmental conditions, such as nutrient availability and stress signals, can impact *bft* expression. While specific environmental triggers for *bft* have not been fully elucidated, it's known that bacteria often adjust gene expression in response to external stimuli to enhance survival and pathogenicity. Nu-

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trients play an important role in the expression of BFT toxin (Bacteroides fragilis toxin). In particular, the composition of the culture medium used to grow *Bacteroides fragilis* significantly affects the level of *bft* gene transcription and toxin secretion. Fermentation of carbohydrates and other nutrients in the intestine can create conditions that promote optimal *bft* gene expression, which enhances the virulence properties of ETBF strains. These effects are also associated with changes in the microbial community in the intestine and the interaction of bacteria with epithelial cells, where BFT induces inflammatory reactions and disruption of intercellular connections [12, 27].

Additionally, host-derived signals, such as hormones or immune responses, may influence bacterial gene expression, including that of *bft*. The interplay between host environments and bacterial regulatory systems is complex and remains an active area of research.

5. CLINICAL RELEVANCE AND DISEASE ASSOCIATION

ETBFs that produce the *Bacteroides fragilis* toxin (BFT) differ from typical commensal bacteria in their capacity to induce inflammation and diarrhoea. There has been much interest in the *B. fragilis* enterotoxin (BFT), especially concerning colorectal cancer and the potential for gastrointestinal epithelial injury. This damage may also affect aberrant gastrointestinal tract illnesses, such as inflammatory bowel disease and autoimmune disorders, by permitting localized translocation of gastrointestinal contents beyond the epithelial barrier. BFT was initially identified in relation to diarrheal illness in neonatal lambs and thereafter in other species. *B. fragilis* is acknowledged as a contributor to diarrhea in humans, particularly in children over one year of age; nonetheless, asymptomatic carriage of BFT-positive *B. fragilis* may reach up to 40% in stool samples and 50–55% in mucosal tissue samples [28].

Enterotoxigenic *Bacteroides fragilis* (ETBF) promotes the development of intestinal inflammation and colorectal cancer (CRC). Cao et al. in their research indicates that ETBF suppresses the miR-149-3p microRNA contained in exosomes, thereby facilitating CRC cell proliferation and inflammation. They discovered that the downregulation of miR-149-3p is regulated by Methyltransferase-like 14 (METTL14) -mediated m6A methylation, resulting in the activation of alternative splicing factors, including PHD Finger Protein 5A (PHF5A). These strategies increase the inflammatory response via T helper cell type 17 (Th17) development. The findings underscore the significance of miR-149-3p as a prospective diagnostic and therapeutic biomarker for individuals with inflammatory bowel disorders and colorectal cancer. Moreover, Cao et al. in their article defines the correlation between ETBF and inflammatory bowel diseases (IBD), namely ulcerative colitis (UC) and Crohn's disease (CD). The concentration of microRNA miR-149-3p in exosomes of patients with inflammatory bowel disease (IBD) is markedly diminished and negatively correlates with the quantity of enterotoxigenic *Bacteroides fragilis* (ETBF), suggesting its involvement in pathophysiology. Exosomal miR-149-3p levels were decreased in individuals with active inflammatory bowel disease compared to those in remission, indicating its potential as a biomarker for evaluating disease activity. Furthermore, ETBF facilitates Th17 cell development via exosomes containing miR-149-3p, augmenting inflammatory processes and establishing conditions conducive to the chronic inflammation typical of IBD [29, 30].

Jamal et al. examined ETBF strains in extraintestinal infections, including bacteremia, intra-abdominal infections (IAI), lower respiratory tract infections (LRTI), abscesses, and wound infections. Among 256 *B. fragilis* isolates, 38.3% tested positive for *bft*, with the *bft*-1 subtype being the predominant variant at 73.5%. Toxin-positive isolates were more prevalent in intra-abdominal infections (39.8%) and lower respiratory tract infections (35.7%) and exhibited heightened resistance to antibiotics, including clindamycin (62%), imipenem (9%), and tigecycline (11%), surpassing the resistance levels of *bft*-negative pathogens. The findings underscore the significance of ETBF as an extra-intestinal pathogen, its considerable antibiotic resistance, and the necessity for additional research to formulate optimum treatment options [31].

6. EXPERIMENTAL TOOLS AND METHODS FOR STUDYING THE *BFT* GENE

Researchers have created diverse experimental instruments and methodologies to investigate the *bft* gene and its related toxin. The cloning and sequencing of the *bft* gene from the VPI 13784 strain facilitated the application of particular PCR primers to ascertain the presence and quantity of the gene in clinical samples [32]. This has facilitated the investigation of the prevalence of enterotoxigenic *B. fragilis* strains in colorectal cancer patients, which has been determined to be greater than in control groups.

Methods for *bft* Gene Identification include:

- The Polymerase Chain Reaction (PCR) is utilised to identify the presence of the *bft* gene in bacterial isolates. Multiplex PCR tests have been established to identify and distinguish among the three recognised *bft* subtypes [33].
- Quantitative PCR (qPCR): Real-time qPCR facilitates the detection of *bft* gene copies in samples, offering insights regarding bacterial load. This technique has been utilised to identify *bft* subtypes in faecal specimens from persons both with and without diarrhoea. The developed RT-PCR method demonstrated high accuracy and speed for studying *bft* subtypes, which contributes to a better understanding of their epidemiological significance [34].
- Digital PCR (dPCR) provides accurate quantification of the *bft* gene, improving detection sensitivity, particularly in samples with low bacterial concentrations. Comparative analyses have assessed the effectiveness of standard PCR, qPCR, and dPCR in identifying the *bft* gene [35].
- *In Vitro* and *In Vivo* Models for Investigating *bft* Effects. In Vitro Models: Cultured human colonic epithelial cells are frequently utilised to evaluate the effects of BFT on cellular shape, barrier integrity, and inflammatory responses. These models clarify the toxin's mechanisms at the cellular level. In Vivo Models: Animal models, especially mice, are employed to investigate the pathogenic consequences of ETBF colonisation. These mice have shown that ETBF can provoke colitis and modify intesti-

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nal permeability, offering insights into disease pathways [36]. In vitro and in vivo models are crucial instruments for investigating the interactions among microbiota, cancer, and nanomedicine, each with distinct advantages and constraints. In vitro models offer a controlled, economical, and reproducible setting for examining particular interactions among microbiota, cancer cells, and nanomedicines; nevertheless, they are deficient in systemic complexity, physiological significance, and immune system influences. Conversely, in vivo models provide a comprehensive perspective by integrating immune responses, long-term consequences, and authentic tumour microenvironments; nonetheless, they entail elevated costs, ethical dilemmas, biological variability, and restricted human applicability owing to interspecies variances. Integrating the advantages of both methodologies facilitates thorough research, connecting preliminary mechanistic studies with intricate, clinically pertinent investigations, thus advancing the development of efficacious nanomedicine-based cancer therapeutics [37].

Utilising these tools and models improves our comprehension of the *bft* gene's function in *Bacteroides fragilis* pathogenicity and its consequences for human health.

7. CURRENT RESEARCH TRENDS IN PATHOGENIC *B. FRAGILIS*

Microbiome Interactions: Recent research has investigated the impact of BFT expression on the colonisation and persistence of *B. fragilis* inside the host microbiome. BFT production is associated with the bacterium's capacity to create a niche in the colonic lamina propria, which may influence prolonged colonisation and illness results. The research of Craig et al. indicates that BFT expression enables enterotoxigenic *B. fragilis* (ETBF) strains to infiltrate the lamina propria of the intestinal mucosa, hence conferring a competitive advantage within the microbiota. This capability arises from the metalloprotease activity of BFT, which compromises the epithelial barrier, elevates the quantity of goblet cells, and establishes routes for bacterial ingress. This adaptation primarily occurs during the pre-weaning phase, when the gut microbiota remains unstable, and is further amplified by antibiotic treatment in adulthood. The findings underscore the significance of BFT for the competitiveness of ETBF, potentially affecting long-term host health, including the risk of chronic inflammation or cancer [38, 39].

Diagnostic Innovations: Initiatives are in progress to create diagnostic instruments aimed at BFT for the early identification of ETBF-associated disorders. Research has identified diagnostic nanobodies targeting BFT, presenting opportunities for enhanced diagnostics. Guo et al. (2023) detailed the development of nanobodies for detecting *Bacteroides fragilis* toxin (BFT) in their publication titled «Screening and epitope characterisation of diagnostic nanobody against total and activated *Bacteroides fragilis* toxin.» The authors cloned and expressed BFT1 in *E. coli*, immunised alpacas to acquire specific nanobodies, and constructed a phage display library, isolating nanobodies Nb2.82 and Nb3.27. Nb2.82 interacts with the prodomain of BFT1, while Nb3.27 associates with its catalytic domain. Their strong affinity was validated using isothermal calorimetry and crystallographic analysis. The resultant nanobodies exhibit great specificity and hold promise for the development of diagnostic testing systems, hence facilitating new opportunities for the early detection of disorders linked to ETBF [7].

Addressing these information deficiencies and investigating therapeutic strategies aimed at the *bft* gene or its products are essential measures for alleviating the pathogenic effects of ETBF and enhancing clinical results.

8 FUTURE PERSPECTIVES AND CHALLENGES

The *bft* gene of *Bacteroides fragilis*, which encodes the *Bacteroides fragilis* toxin (BFT), is crucial to the bacterium's pathogenicity. Nonetheless, numerous facets of its functionality and regulation remain unclear.

Deficiencies in Comprehending the *bft* Gene

The specific transcriptional and post-transcriptional regulatory mechanisms controlling *bft* expression remain inadequately understood. Grasping these systems is essential for understanding how *B. fragilis* regulates toxin production in reaction to diverse stimuli.

The influence of environmental factors, including host-derived signals and microbial interactions, on *bft* expression remains weakly examined. Understanding these influences may illuminate the factors that facilitate toxin formation.

The complex interactions between BFT and host cellular pathways, encompassing the individual receptors implicated and subsequent effects, necessitate additional research.

Potential for targeting the *bft* gene or its products in therapy.

Analysis of the BFT structure opens up opportunities for the development of new allosteric inhibitors that, unlike classical metalloprotease inhibitors, provide higher selectivity, reduced risk of side effects and preservation of normal intestinal microbiota, since their action is directed exclusively at the ETBF toxin. Thus, in the study by Jimenez-Alesanco et al., specific inhibitors of the BFT-3 toxin were identified that are capable of blocking its activity without affecting the beneficial intestinal microflora. The discovered inhibitors bind to an allosteric site located on the surface of the catalytic domain (CD) of BFT-3, opposite the active center. This site is called the distal allosteric exosite and is located approximately 25 Å from the active center of the enzyme. Binding of inhibitors to this exosite causes conformational changes that prevent proper activation of the toxin. In particular, these compounds stabilize the partially unfolded, zinc-independent form of the toxin precursor (proBFT-3), thereby preventing zinc binding in the active site and inhibiting the catalytic activity of the enzyme. This mechanism differs from the traditional approach in which inhibitors interact directly with the active site. Among the studied compounds, three promising inhibitors (C-4, C-9, and C-10) were identified that showed high efficacy in both biochemical tests and cellular models. These compounds significantly reduced BFT-3 activity and prevented pathologically associated degradation of E-cadherin. Thus, these inhibitors are promising candidates for the treatment of ETBF-associated diseases, including inflammatory bowel diseases and colorectal cancer, without disrupting the composition of the normal intestinal microbiota [20].

The study by Ko et al. (2023) examined the effects of Bac-

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teroides fragilis enterotoxin (BFT) on autophagy and apoptosis in HCT-116 intestinal epithelial cells. The results showed that BFT initiates an autophagic response through the AMPK–FoxO3a signaling pathway, which contributes to the suppression of apoptosis at the early stages of toxin exposure. These results suggest a potential protective role for autophagy in intestinal epithelial cells during infection with enterotoxigenic B. fragilis (ETBF) strains [40].

CONCLUSION

The *bft* gene in Bacteroides fragilis is a key pathogenicity factor of enterotoxigenic bacterial strains (ETBF), contributing to the development of inflammatory bowel diseases and colorectal cancer via its zinc-dependent metalloprotease activity. The diversity of *bft* allelic variants (*bft*-1, *bft*-2, and *bft*-3) demonstrates the genetic diversity of ETBF and differences in its pathogenicity. BFT maintains epithelial integrity by altering E-cadherin, activates inflammatory signaling pathways, and promotes oncogenic processes, highlighting its importance in the pathogenesis of gastrointestinal diseases.

Despite extensive studies, the precise regulatory mechanisms of *bft* expression and its interactions with host cellular pathways remain poorly understood. The impact of changing environmental conditions and microbial community dynamics on *bft* expression requires further analysis. The development of diagnostic technologies such as PCR detection and nanobody-based biosensors opens new perspectives for the early diagnosis of ETBF-related diseases. In addition, the development of allosteric inhibitors targeting BFT activity represents a promising avenue for therapeutic intervention while preserving normal gut microbiota.

Future research should focus on studying the molecular mechanisms of *bft* regulation, microbiome-host interactions, and creating targeted therapeutic strategies to reduce the disease burden caused by ETBF. Filling these knowledge gaps will enhance the ability to effectively combat ETBF infections and improve patient outcomes.

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AUTHOR CONTRIBUTIONS

Conceptualization: A.B. and S.K.; Project administration: S.K.; Writing - original draft: A.B., B.K. and S.K.; Writing review and editing: A.B., E.Zh. and S.K.

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BACTEROIDES FRAGILIS ТОКСИН ГЕНІ (*BFT*): ОНЫҢ ВИРУЛЕНТТІЛІКТЕГІ, РЕТТЕУ ЖӘНЕ АУРУЛАРДАҒЫ РӨЛІ

*** А. Бекбаева[1,2], Б.С. Қоңыр[3], Е.В. Жолдыбаева[1], С.С. Кожахметова[1]**

[1]Ұлттық биотехнология орталығы, Қорғалжын тас жолы, 13/5, Астана қ., 010000, Қазақстан;
[2]Л.Н.Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев к-сі, 2, Астана қ., 010000, Қазақстан
[3]Әл-Фараби атындағы Қазақ Ұлттық университеті , Әл-Фараби даңғылы, 71, Алматы қ., 050040,
** bekbayeva@biocenter.kz*

АННОТАЦИЯ

Bacteroides fragilis токсинінің (*bft*) гені әртүрлі асқазан-ішек ауруларымен, соның ішінде колоректальды обыр мен ішектің қабыну ауруларымен тығыз байланысты энтеротоксигенді *Bacteroides fragilis* (*ETBF*) штаммдарының вирулент-тілігінде маңызды рөл атқарады. Энтеротоксигенді *Bacteroides fragilis* (ETBF) штаммдарында *Bft* генінің болуы және экспрессиясы эпителий тосқауылын бұзу, созылмалы қабынуды ынталандыру және канцерогенезге әсер ету арқылы ETBF патогенділігіне айтарлықтай ықпал етеді. Бұл шолуда *bft* генінің генетикалық құрылымы, аллельдік вариациялары және *bft* реттеу механизмдері жан-жақты талдау келтірілген, оның аурудың өршуіндегі рөлін көрсетеді. Токсин өзінің патогендік әсерін жасуша адгезиясының маңызды құрамдас бөлігі болып табылатын Е-кадеринді ыдырату арқылы көрсетеді, осылайша эпителий тұтастығын бұзады және бактериялардың енуін жеңілдетеді. Сонымен қатар, BFT қабыну реакциялары мен жасушалық трансформацияны басқаратын NF-kB және MAPK сияқты негізгі жасушаішілік сигналдық жолдарды белсендіреді. Бұл шолуда сонымен қатар диагностикалық әдістер мен инновациялық терапевтік тәсілдердегі жетістіктер, соның ішінде BFT белсенділігін блоктауға арналған аллостериялық ингибиторлардың дамуы талқыланады. *Bft* реттеуі мен функциясын түсінудегі елеулі прогреске қарамастан, оның молекулалық өзара әрекеттесуі мен қоршаған орта триггерлеріне қатысты білімдегі маңызды олқылықтар сақталады. Болашақ зерттеулер ETBF байланысты аурулардағы клиникалық нәтижелерді жақсартатын мақсатты терапияны әзірлеуді жеңілдету үшін осы механизмдерді түсіндіруге бағытталуы керек.

Кілт сөздер: *Bacteroides fragilis* токсині (*bft*); энтеротоксигенді *Bacteroides fragilis* (ETBF); эпителий тосқауылы-ның бұзылуы; NF-kB жолы; тоқ ішек қатерлі ісігі; аллостериялық ингибиторлар; терапиялық стратегиялар.

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ГЕН ТОКСИНА *BACTEROIDES FRAGILIS (BFT)*: ЕГО РОЛЬ В ВИРУЛЕНТНОСТИ, РЕГУЛЯЦИИ И ЗАБОЛЕВАНИЯХ

*** А. Бекбаева[1,2], Б.С. Коныр[3], Е.В. Жолдыбаева[1], С.С. Кожахметова[1]**

[1]Национальный центр биотехнологии, Кургальжинское шоссе, 13/5, г. Астана, 010000, Казахстан;
[2]Евразийский национальный университет имени Л.Н. Гумилева, ул. Сатпаева, 2, г. Астана, 010000, Казахстан
[3]Казахский национальный университет имени аль-Фараби, проспект аль-Фараби, 71,г. Алматы, 050040, Казахстан;
** bekbayeva@biocenter.kz*

АННОТАЦИЯ

Ген токсина *Bacteroides fragilis (bft)* играет решающую роль в вирулентности энтеротоксигенных штаммов *Bacteroides fragilis* (ETBF), которые тесно связаны с различными желудочно-кишечными расстройствами, включая колоректальный рак и воспалительные заболевания кишечника. Присутствие и экспрессия *bft* вносят значительный вклад в патогенность ETBF, нарушая эпителиальный барьер, способствуя хроническому воспалению и влияя на канцерогенез. В этом обзоре представлен всесторонний анализ генетической структуры, аллельных вариаций и регуляторных механизмов *bft*, подчеркивающий его роль в прогрессировании заболевания. Токсин оказывает свое патогенное действие, расщепляя Е-кадгерин, критический компонент клеточной адгезии, тем самым нарушая целостность эпителия и облегчая бактериальную инвазию. Кроме того, BFT активирует ключевые внутриклеточные сигнальные пути, такие как NF-kB и MAPK, которые управляют воспалительными реакциями и клеточной трансформацией. В этом обзоре также рассматриваются достижения в диагностических методах и инновационных терапевтических подходах, включая разработку аллостерических ингибиторов, предназначенных для блокирования активности BFT. Несмотря на значительный прогресс в понимании регуляции и функции *bft*, сохраняются существенные пробелы в знаниях относительно его молекулярных взаимодействий и экологических триггеров. Будущие исследования должны

быть направлены на выяснение этих механизмов для содействия разработке таргетной

терапии, в конечном итоге улучшающей клинические результаты при заболеваниях, связанных с ETBF.

Ключевые слова: токсин *Bacteroides fragilis* (*bft*); энтеротоксигенный *Bacteroides fragilis* (ETBF); нарушение эпи-телиального барьера; путь NF-kB; колоректальный рак; аллостерические ингибиторы; терапевтические стратегии.