Advances in drug resistance and resistance mechanisms of four colorectal cancer-associated enteric bacteria (#108964)

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Advances in drug resistance and resistance mechanisms of four colorectal cancer-associated enteric bacteria

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Colorectal cancer (CRC) is a common malignant tumor in the gastrointestinal tract with inconspicuous early symptoms, high morbidity and mortality, and poor prognosis. Enteric bacteria are present in the human intestinal system and have certain functions, which include the integrity of the epithelial barrier and the enhancement of protective immune responses. The etiology colorectal cancer is unknown, and the instability of the intestinal microbiome is one of the main factors in the development of colorectal cancer, which mainly includes *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis*. However, the long-term use and abuse of antibiotics have made the problem of drug resistance a difficult problem that currently plagues the regulation of enteric bacteria, as well as a thorny issue in the prevention and treatment of CRC. In this review, we elucidated the drug resistance of four colorectal cancer-associated enteric bacteria, namely *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis*, and discussed the common and different aspects of the resistance mechanisms of the four intestinal bacteria, with the aim of providing a basis for the prevention and control of CRC.

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ABSTRACT

Colorectal cancer (CRC) is a common malignant tumor in the gastrointestinal tract with inconspicuous early symptoms, high morbidity and mortality, and poor prognosis. Enteric bacteria are present in the human intestinal system and have certain functions, which include the integrity of the epithelial barrier and the enhancement of protective immune responses. The etiology colorectal cancer is unknown, and the instability of the intestinal microbiome is one of the main factors in the development of colorectal cancer, which mainly includes *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis*. However, the long-term use and abuse of antibiotics have made the problem of drug resistance a difficult problem that currently plagues the regulation of enteric bacteria, as well as a thorny issue in the prevention and treatment of CRC. In this review, we elucidated the drug resistance of four colorectal cancer-associated enteric bacteria, namely *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis*, and discussed the common and different aspects of the resistance mechanisms of the four intestinal bacteria, with the aim of providing a basis for the prevention and control of CRC.

Keywords colorectal cancer, *Bacteroides fragilis*, *Fusobacterium nucleatum*, enterotoxin-producing *Escherichia coli*, *Enterococcus faecalis*, drug resistance mechanism

INTRODUCTION

In recent years, the incidence and mortality of colorectal cancer (CRC) have been high (Fig. 1(Bray et al., 2018; Fitzmaurice et al., 2019; Kocarnik et al., 2022; Sung et al., 2021)), and the incidence cases of colorectal cancer worldwide have reached 1.833 million cases and 896,000 deaths in 2017 alone, and the incidence cases of colorectal cancer in 2019 once rose to 2.17 million cases and deaths of about 1.09 million cases. The incidence cases in 2020 will be about 1.93 million cases and deaths will be about 940,000 cases. In April 2024, the International Agency for Research on Cancer (IARC) published the latest global cancer statistics for 2022 in the《CA: A Cancer Journal for Clinicians》, which showed that there were approximately 1,926,000 colorectal cancer cases and 904,000 deaths in 2022(Hossain et al., 2022; Yuxin, 2024). The pathogenesis and progression of colorectal cancer involve a number of mechanisms, such as abnormal cell proliferation and differentiation, invasion of neighboring tissues and distant metastasis, and a series of pathophysiological mechanisms, in which many genes and signaling pathways are involved in the pathogenesis and progression of colorectal cancer, but the etiology of colorectal cancer is unclear(Ionescu et al., 2023), this is probably the main reason for the high prevalence of this type of disease, as the unknown etiology limits the effectiveness of its prevention and treatment strategies, leading to high morbidity and mortality rates.

As early as the 1970s, studies have found that gut microbes are closely related to the development of CRC(Mentella et al., 2020). In recent years, the correlation between gut

microbiome profiles and colorectal adenoma-cancer sequences has been validated based on high-throughput sequencing and population-based big data analysis, further confirming that changes in intestinal flora play an important role in colorectal cancer development and progression(Tilg et al., 2018). Among them, *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis* are most closely associated with the development of CRC(Bonnet et al., 2014; Feng et al., 2015; Nakatsu et al., 2015; Williamson et al., 2022), The ability to effectively regulate the abundance of *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis* in the intestinal tract has become a key component in the prevention and control of CRC. Along with the long-term use and abuse of antibiotics, the problem of drug resistance has become a difficult problem in the regulation of intestinal flora, and also a thorny issue in the prevention and control of CRC. Currently, there are few reports on the drug resistance of the four CRC-associated intestinal flora and the mechanism of drug resistance(Liu et al., 2021). The aim of this review is to provide an in-depth discussion on the drug resistance of four colorectal cancer-associated enteric bacteria, namely *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis*, as well as the mechanisms of drug resistance, with the aim of providing a rationale for the prevention and control of CRC.

SURVEY METHODOLOGY

This review is the result of a systematic literature search on PubMed and Web of Science. It aimed to find articles related to drug resistance as well as mechanisms of resistance in four colorectal cancer-associated intestinal flora, namely *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis*, for the period up to 2024. Articles used different combinations of search terms including “colorectal cancer or colorectal tumor or CRC”, “(gastrointestinal microbiome or gut microbiota) and (colorectal cancer or colorectal tumor or CRC)”, “(*Bacteroides fragilis* or BF) and (colorectal cancer or colorectal tumor or CRC)”, “*Escherichia coli* and (colorectal cancer or colorectal tumor or CRC)”, ”(*Fusobacterium nucleatum* or Fn) and (colorectal cancer or colorectal neoplasia or CRC)”, “*Enterococcus faecalis* and (colorectal cancer or colorectal neoplasia or CRC)”, “(*Bacteroides fragilis* or BF) and antibiotics”, “*Escherichia coli* and antibiotics”, “*(Fusobacterium nucleatum* or Fn) and antibiotics”, “*Enterococcus faecalis* and antibiotics”, “*Bacteroides fragilis* or BF) and drug resistance”, “*Escherichia coli* and drug resistance”, “(*Fusobacterium nucleatum* or Fn) and drug resistance”, “*Escherichia coli* and drug resistance”, “*Enterococcus faecalis* and drug resistance”, “(*Bacteriophage fragilis* or BF) and drug resistance mechanisms”, “*Escherichia coli* and resistance mechanisms”, “(*Fusobacterium nucleatum* or Fn) and resistance mechanisms”, and “*Enterococcus faecalis* and resistance mechanisms”. Meanwhile, we reviewed the main resistance mechanisms of the four colorectal cancer-associated intestinal flora, namely *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis*, including mutation of resistance genes, transfer of horizontal genes, and resistance mechanisms of the exocytosis pump street. We used a search strategy to obtain the titles and abstracts of the relevant studies that we initially screened and retrieved the full text. We also reviewed relevant

references in the articles to ensure the comprehensiveness of the studies.

OVERVIEW OF COLORECTAL CANCER-ASSOCIATED ENTERIC BACTERIA

In recent years, *Fusobacterium nucleatum(F. nucleatum)*, pathogenic *Escherichia coli(E. coli)*, enterotoxigenic *Bacteroides fragilis(B. fagilis)*, and *Enterococcus faecalis(E. faecalis)* have been most widely reported in colorectal cancer-associated enteric bacteria (Fig. 2(Dougherty & Jobin, 2023; Song et al., 2020)). Epidemiologic studies have found a significant positive correlation between *Fusobacterium nucleatum* abundance and CRC stage, preferentially enriched in advanced colorectal cancer tissues(Dougherty & Jobin, 2023; Xu et al., 2021a). Numerous studies have shown that *Fusobacterium nucleatum* colonization promotes tumor growth in ApcMin/$^{+}$ mice(Chen et al., 2020; Lin et al., 2020; Wang & Fang, 2023). Pathogenic *Escherichia coli* (pks+ *E. coli*) was more prevalent in stool or tissue samples from patients with colorectal cancer compared to patients with inflammatory bowel disease (IBD) or healthy controls(Dubinsky et al., 2020). Preclinical studies based on the ApcMin/$^{+}$ mouse model suggest that ETBF colonization promotes colitis and distal colon tumor formation(Dougherty & Jobin, 2023; Song et al., 2020). *Enterococcus faecalis* is one of the most common commensal enterococci found in human feces, and studies have shown that it induces migration and invasion of colorectal cancer cells(Williamson et al., 2022)。

OVERVIEW OF DRUG RESISTANCE IN FOUR SPECIES OF ENTERIC BACTERIA

Antibiotics were first discovered in the 1920s, and the 1950s and 1960s were the golden years of antibiotic development (Fig. 3(Hutchings et al., 2019; Lewis, 2020)), when antibiotics were once the first choice in clinical protocols for dealing with harmful bacteria(Ramirez et al., 2020). Among them, research on four types of antibiotics related to colorectal cancer has never stopped, such as cephalosporin antibiotics, which have developed five generations of drugs with different antibacterial activities(2012b). However, with the emergence of antibiotic abuse and other phenomena in recent years, the reports of colorectal cancer-associated enteric bacteria resistance to antimicrobial drugs have gradually increased. Among the existing reports, the studies on the resistance mechanisms of the above four bacteria are mostly related to their drug-resistant genes. Based on this, this paper firstly summarizes the resistance profiles of the above four colorectal cancer-associated bacteria and the resistance mechanisms mediated by resistance genes, and the results are shown in Table 1(Alauzet et al., 2019; Barlaam et al., 2019; Bartha et al., 2011; Bush & Jacoby, 2010; Conceição et al., 2014; Edwards & Read, 2000; Eitel et al., 2013; Goldstein, 2014; Grossman, 2016; He et al., 2016; Hiraga et al., 2008; Hussain et al., 2021; Huys et al., 2004; Johnsen et al., 2017; Kierzkowska et al., 2019; Li et al., 2022; Naselli et al., 2022; Patel et al., 2023; Schwarz et al., 2021; Tamma et al., 2019; Voha et al., 2006; Wang et al., 2000; Yekani et al., 2022).

Antibiotic Resistance of B. fagilis

Studies have shown that enterotoxigenic *Bacteroides fragilis* is resistant to currently used antimicrobial drugs to varying degrees(Yuran, 2020). Researchers conducted drug sensitivity tests on the isolated strains of *Bacteroides fragilis*, and the results showed that the resistance rate of *Bacteroides fragilis* to metronidazole was 1.2%; to chloramphenicol was 6.1%; and to carbapenems had reached 22.0%(Junhua, 2021). Metronidazole is one of the most commonly used antibiotics for the treatment of anaerobic infections, especially those of Mimicronium fragilis. Carriage of the nim gene is responsible for the development of resistance to metronidazole in this anaerobic bacterium as shown in Table 1.

Antibiotic Resistance of F. nucleatum

Carbapenems, β-lactam/β-lactamase inhibitor combinations, metronidazole, clindamycin, and moxifloxacin are used in clinical practice for the treatment of infections caused by Fusobacterium(Shilnikova & Dmitrieva, 2015). Studies have demonstrated that *F. nucleatum* exhibits a high degree of resistance to tetracycline, doxycycline, metronidazole, clindamycin and erythromycin(Ardila et al., 2023; Ardila & Vivares-Builes, 2022; Bullman et al., 2017).

Antibiotic Resistance of E. coli

A resistance analysis based on isolates showed that *E. coli* was 85.0% resistant to ampicillin and 55.1% resistant to ciprofloxacin, 53.9% resistant to ceftriaxone, 52.7% resistant to cotrimoxazole, and 52.1% resistant to levofloxacin(Zhen, 2018). Studies have shown that *E. coli* is resistant to the usual quinolone antibiotics(Fritzenwanker et al., 2018). This shows that *E. coli* is resistant to all common antibiotics. Neonatal *Escherichia coli* invasive isolates from developing countries have been reported to be up to 100% resistant to ampicillin and up to 90% resistant to gentamicin(Cole et al., 2019). In addition, the frequent use of antibiotics and their combination has led to the gradual development of multidrug resistance in *E. coli*, and the results of a multidrug-resistant *E. coli* showed that the prevalence of multidrug-resistant *E. coli* isolates was 57.3% (47/82), with 39 modes of resistance(Kallau et al., 2018).

Antibiotic Resistance of E. faecalis

The results of a clinical isolation of *Enterococcus faecalis* showed that among 74 clinical isolates of *Enterococcus faecalis*, the antibiotics with a high degree of resistance were mainly tetracycline and erythromycin, with a resistance rate of 89.2% and 73.0%, respectively; followed by quinolones ciprofloxacin and levofloxacin, with a resistance rate of 39.2% and 36.5%, respectively; once again, the high concentration of gentamicin has a resistance rate of 32.4%(Hong, 2019). The results of the analysis showed that most of the *Enterococcus faecalis* isolates had a multidrug resistance pattern(Farman et al., 2019). Results of an antibiotic resistance study of *Enterococcus faecalis* isolated from clinical and commensal samples from

Iran showed a multidrug resistance rate of 69.4% in *Enterococcus faecalis*(Ghaziasgar et al., 2019)。

ANTIBIOTIC RESISTANCE MECHANISMS IN FOUR INTESTINAL BACTERIA

With the extensive use of antibiotics and long-term use, many bacteria have gradually developed different degrees of resistance to different antibiotics, and their resistance mechanisms have also become complicated. Exploring the mechanism of bacterial resistance can help to improve antibiotics and develop new drugs, and this review will elaborate on the resistance mechanisms of four colorectal cancer-associated intestinal bacteria.

Antibiotic Resistance Mechanisms in B. fragilis

It has been reported that isolates of *Bacteroides fragilis* have multiple resistance determinants, such as multidrug efflux pumps, cfiA and nimB genes, and activating insertion sequences(Boyanova et al., 2019).

Drug-resistant gene-mediated resistancenim

Protein is a determinant of metronidazole resistance, and the nim gene encoding the nim protein is present on plasmids or chromosomes(Haggoud et al., 1994). Regarding the mechanism of how the nim gene causes bacterial resistance to metronidazole, experts and scholars believe that the nim protein, which has the properties of a nitroreductase enzyme, reduces metronidazole to a nontoxic aminopyrimidazole by transferring six of its own electrons to the nitro group of metronidazole, thus leading to the development of bacterial resistance to metronidazole(Deyan, 2023). Resistance to carbapenems in isolates of *Bacteroides fragilis* is mainly due to the presence of the cfiA gene, which encodes a metallo-β-lactamase (MBL) whose main mechanism of action is to inhibit β-lactam antibiotic activity by hydrolyzing the amide moiety of the β-lactam ring(Yekani et al., 2022), cfiA-positive strains usually show resistance to almost all β-lactam antibiotics(Wang et al., 2023). The results of the study showed that cfiA was present in all carbapenem-resistant isolates of *Bacteroides fragilis*(Gao et al., 2019). It has been shown that in most strains of *B. fragilis*, the cfiA gene is not always highly expressed and may be silenced, but is highly expressed when certain Insertion Sequence (IS) elements or some non-IS-mediated activation mechanism is mutated upstream of it, leading to high drug resistance in *B. fragilis*(Yekani et al., 2022). Among the β-lactam antibiotic resistance in *B. fragilis* mainly associated with the cepA gene and cfxA it carries, Niestępski S et al. showed that 55 out of 123 (44.72%) BFG strains showed phenotypic resistance to ampicillin, and that 23 out of 55 (41.82%) resistant strains carried the β-lactam (cepA and cfxA) resistance genes(Niest pski et al., 2019). In addition, the researchers found the tetracycline resistance gene tetQ, macrolide and clindamycin resistance genes ermF in *B. fragilis*(Junhua, 2021). A genotyping study of clinical isolates of multidrug-resistant *B. fragilis* from India showed that these strains tended to express

combinations of two or more resistance genes, e.g., two different resistance genes were coexisting in 25.8% of the strains, three different resistance genes were coexisting in 33.8% of the strains, and four different resistance genes were coexisting in 3.2% of the strains, with combinations of ermF and cepA being more common. The combination of ermF and cepA was more common, while cfiA, ermF and cepA were more frequently present in strains containing three resistance genes(Colney et al., 2021). In summary, the major resistance genes in *B. fragilis* were nim, cfiA, cepA, cfxA, tetQ, and ermF; and the major genes that led to the development of multimandibular resistance in *B. fragilis* were the simultaneous presence of cfiA, ermF, and cepA in the strain.

Horizontal gene transfer-mediated drug resistance

Acquisition of mobile genetic elements such as plasmids carrying drug resistance genes by bacteria through horizontal gene transfer (HGT) is one of the main ways for them to develop drug resistance(San Millan, 2018). Studies have shown that antibiotic resistance genes can be transferred horizontally by a variety of mechanisms, the heaviest of which are transformation, transduction, and conjugation (Fig. 4)(McInnes et al., 2020).

Resistance gene transformation mainly refers to the uptake of naked DNA from the extracellular environment of *B. fragilis* by *B. fragilis*, which is then admixed into the host genome of the bacterium through homologous recombination(Johnston et al., 2014), As a result, *B. fragilis* has also acquired a corresponding antibiotic resistance. According to the study, the transformation mechanism is largely related to the genome of the recipient bacteria, and these genes or genomes are involved in exogenous DNA uptake and integration into the chromosome of the recipient bacteria(Michaelis & Grohmann, 2023). The discovery of vesicles solved the mystery in the researchers' minds, as free DNA is not stable and its time to remain intact outside the cell is short, which seems to limit the realization of transformation. The study suggests that the transport of drug-resistant genes between bacteria is also linked to membrane vesicles, and that certain drug-resistant genes or β-lactamases may transfer material by fusing with cells(Moura de Sousa et al., 2023). Membrane vesicles are spherical structures of 20-250 nm. Membrane vesicles enable the transmission of drug-resistant genes by fusing with target cells(McInnes et al., 2020). In vitro production of membrane vesicles containing β-lactamases by intrinsically drug-resistant *B. fragilis*, which then fuses with target cells that ingest the membrane vesicles to deliver the corresponding resistance genes(Stentz et al., 2015), This leads to the development of corresponding resistance in the cells of the target bacteria.

The mechanism of transduction of drug-resistant genes mainly refers to the transfer of drug-resistant genes between bacteria via phages, which play a central role in mediating the horizontal transfer of drug-resistant genes(Chiang et al., 2019). According to reports, phage communities are widely present in the human gut(Shkoporov & Hill, 2019), which carry antibiotic resistance genes in large numbers(Debroas & Siguret, 2019). It was found that φB124-14 served as a human gut-specific phage whose original host was *B. fragilis*, and the phage was also known as a mobile macrogenome in the human gut because of its richness in multiple antibiotic resistance

genes(Ogilvie et al., 2012). The abundance of these phages carrying antibiotic resistance genes increased significantly in the human gut after antibiotic treatment(McInnes et al., 2020).

The mechanism of conjugation of resistance genes mainly refers to the transfer of mobile genetic elements such as plasmids and integrative splicing elements from one bacterium to another(McInnes et al., 2020). Conjugative transposons (CTn) are segments of DNA, mobile genetic elements integrated into chromosomes, which are able to move the relevant resistance genes to new locations precisely in the same or different DNA molecules in certain bacterial cells, resulting in the production of the corresponding drug resistance(Boiten et al., 2023; Partridge et al., 2018). It has been reported that the major resistance genes associated with B.fragilis, such as cepA for cephalosporins, ermF for MLSB analogs, and tetQ for tetracyclines, are essentially carried on the chromosome by conjugation transposons(Sóki et al., 2016). Among them, Boiten KE et al. showed that resistance to tetracycline in *B. fragilis* increased from an initial 20% to 80% in 20 years, and that the tetQ gene located on the conjugation transposon may be the underlying mechanism(Boiten et al., 2023). It has been studied that transposons may also undergo mutations during the course of bacterial development, Tn5520 is a transposon that is mobile in *B. fragilis*. The Tn5520-like transposon in the isolate identified by Cao H et al. belongs to two new variants (Tn6995 and Tn6996), which differ from the original Tn5220 in that they have ermF genes, which lead to resistance to streptozotocin(Cao et al., 2022).

Overexpression of bacterial multidrug active efflux systems

Multidrug efflux pumps play an important role in the process of bacterial drug resistance, in which bacteria utilize efflux pumps to reduce the concentration of drugs in their own bodies and develop drug resistance(Huang et al., 2022). Existing studies have identified six drug efflux system superfamilies, namely, the major facilitator super family (MFS), small multidrug resistance (SMR), ATP binding cassette (ABC), resistance nodulation and cell division (RND), multidrug and toxic compound extrusion (MTCE), and resistance nodulation and cell division (RND), multidrug and toxic compound extrusion family (MATE), and proteobacterial antimicrobial compound efflux family (PACE)(Zhouxing, 2022). Among them, the PACE family proteins have a relatively narrow drug-substrate recognition spectrum, which mainly includes some synthetic biocides such as chlorhexidine and acridine yellow, whereas the transporter proteins from the RND superfamily recognize a large number of different antibiotics and biocides(Hassan et al., 2018). According to research, certain exocytosis systems consist of a series of transporter proteins that remove a variety of foreign substrates from the bacterial cell, thus reducing the effects of multiple drugs on the bacteria, and may be referred to as multidrug efflux pumps(Huang et al., 2022). The emergence of multidrug efflux pumps has been reported to be one of the major causes of multidrug resistance in *B. fragilis*, and RND-type efflux pumps and MATE-type efflux pumps are prevalent in wild-type strains of *B. fragilis*(Ghotaslou et al., 2018b). Studies have shown that overexpression of multidrug efflux pumps is increasingly closely associated with bacterial drug resistance during clinical treatment of infections(Deyan,

2023), particularly for the emergence of multidrug-resistant *B. fragilis*: overexpression of the efflux pump plays an important role in the resistance of *B. fragilis* to antimicrobial agents such as β-lactams, fluoroquinolones, tetracyclines, fusidic acid, neomycin, metronidazole, and other virulence compounds, including triclosan, sodium dodecyl sulfate (SDS), and cholestrol salts(Ghotaslou et al., 2018b)。

Mechanisms of Antibiotic Resistance In F. nucleatum

Mechanisms of β-lactamase-mediated antibiotic resistance

It was shown that the FUS-1 enzyme found in *Fusobacterium nucleatum* (*F. nucleatum*) is the first of its class D β-lactamase-producing enzymes(Dupin et al., 2015). Class D β-lactamase genes, often identified as intrinsic resistance determinants in environmental bacteria, occur in removable genetic elements carried by clinically important pathogenic bacteria(Yoon & Jeong, 2021), Reported FUS-1 genotype of *F. nucleatum* from a clinical isolate of human pathogenic *F. nucleatum*(Voha et al., 2006).

Other resistance mechanisms

Studies have shown that exposure to a particular antibiotic interferes with the susceptibility of *F. nucleatum* to several antibiotics and may reduce susceptibility to antibiotics with similar mechanisms of action or the same resistance mechanism(de Souza Filho et al., 2012). de Souza Filho JA et al. showed that selected β-lactam strains were also much less susceptible to chloramphenicol and metronidazole(de Souza Filho et al., 2012). However, it has been shown that while resistance to β-lactam antibiotics in most Gram-negative bacteria is mediated by β-lactamase production, other mechanisms of antibiotic resistance include changes in penicillin-binding proteins, decreased permeability, or increased efflux pump activity(Huemer et al., 2020), Thus, in the study by de Souza Filho JA et al, it was again noted that no significant differences were observed in the antimicrobial drug susceptibility patterns of ampicillin and ampicillin-sulbactam, which suggests that cross-resistance between β-lactams, chloramphenicol, and metronidazole may indicate the induction of common mechanisms of resistance, such as changes in cell wall permeability(de Souza Filho et al., 2012).

Antibiotic Resistance Mechanisms in E. coli

Drug resistance mediated by mutations in drug resistance genes

First, it has been shown that mutations in drug-resistant genes are one of the main mechanisms for the development of drug resistance in *E. coli*, including spontaneous mutations, hypermutations, and adaptive mutations(Pulingam et al., 2022), Among them, Rodríguez-Verdugo A et al. showed that spontaneous mutations can be driven by, for example, interfering with DNA replication, and that resistance to rifampicin in *Escherichia coli* is achieved by

mutations in the rpoB gene encoding an RNA polymerase(Rodríguez-Verdugo et al., 2013); hypermutation confers an evolutionary advantage to the bacterial species during adaptation to new environments or stressful conditions(Oliver & Mena, 2010); adaptive mutations refer to mutations at the transcriptional level that occur in the bacterial genome to adapt to changes in the survival environment, and when the environmental stress is lifted, the bacterial genome returns to its original condition(Fernández & Hancock, 2012; Pulingam et al., 2022).

According to the study, AmpR and AmpC are encoded by the ampR and ampC genes, respectively, suggesting that the ampR and ampC genes are related, and that AmpR serves as a transcriptional activator that binds to the cis-trans region upstream of the ampC gene promoter, thus acting to regulate AmpC(Philippon et al., 2022). Since the transcriptional regulator (AmpR) expressing AmpC is reportedly not present in *E. coli*, by what mechanism is the AmpC gene regulated? Haenni M et al. showed that there are five highly conserved mutations in the promoter of AmpC, while the mutations in the attenuator are much more frequent, which are mainly attributed to spontaneous mutations in the promoter and attenuator(Haenni et al., 2014; Kakoullis et al., 2021). This suggests to us that using promoter or attenuator mutation sites as drug targets may be an effective strategy to deal with AmpC-type *E. coli* drug resistance.

Hypermutagenic bacteria are microorganisms that have a stronger affinity for spontaneous mutations due to DNA repair defects or avoidance system errors(Oliver & Mena, 2010), resulting in greater adaptability to antibiotics. Hypermutagenic phenotypes of *E. coli* have been reported earlier(Denamur et al., 2002). According to studies, the mismatch repair system (MMR) is particularly important in the phenomenon of hypermutation, as it is not only one of the main causes of bacterial hypermutation, but also one of the main factors in the progression of colorectal cancer(Jin & Sinicrope, 2022). It has been shown that the most commonly mutated gene in strains with hypermutated phenotypes of *E. coli* is the mutHLS gene of the DNA methyl-orientation MMR pathway(Ellington et al., 2006).

Adaptive mutation denotes a temporary increase in the viability of a bacterium when it is attacked by an antibiotic, mainly due to changes in the bacterial genome or protein expression as a result of other environmental factors to which the bacterium is subjected, such as the nutrient conditions to which it is subjected or the sub-inhibitory concentration of the antibiotic itself(Fernández & Hancock, 2012). Simply put, adaptive mutations may be the induced mechanism by which bacteria produce genetic variability in a stressful state(McKenzie et al., 2000). It was shown that *E. coli* exposed to sublethal concentrations of streptomycin induced the expression of recA- and umuDC-independent mutant phenotypes on transfected M13 single-stranded DNA(Pulingam et al., 2022).

β-lactamase-mediated drug resistance

Another major mechanism by which *E. coli* develops resistance to β-lactam antibiotics is

mediated by β-lactamase activity(Bush, 2018). The Ambler system based on sequence information indicates that β-lactamases are classified into four distinct classes called A, B, C, and D(Tooke et al., 2019). Epidemiologic investigations have shown that the prevalent strains have different rates and mechanisms of resistance at different times, in different regions, and in different populations(Xing, 2020). Strains with class A extended-spectrum β-lactamase genotypes (AmpA-type β-lactamases) are the most common, and class C β-lactamase (AmpC-type β-lactamases) genotypes are highly resistant, which has attracted extensive interest from researchers(Poirel et al., 2018).

Class A beta-lactamases include penicillinase type 1 (PC1)(Tooke et al., 2019), TEM (named after Temoneira, the patient from whom the isolate originated)(Datta & Kontomichalou, 1965), Sulfhydryl Variant (SHV)(Chaves et al., 2001), Cefotaximase (CTX-M) , (Bauernfeind et al., 1990)and Klebsiella pneumoniae carbapenemases (KPC) (Rapp & Urban, 2012), it has been shown that the key to the ability of these class A β-lactamases to render antibiotics less effective is their ability to propagate on plasmids and other removable genetic elements in a range of Gram-negative bacteria, as well as the fact that they broaden their spectrum of activity as new substrates are discovered in the clinic, which is also referred to in clinical terms as “extended-spectrum” phenotypic beta-lactamases (ESBLs)(Tooke et al., 2019). The production of extended-spectrum β-lactamases is the main reason for the resistance of *Escherichia coli* to β-lactam antibiotics, extended-spectrum β-lactamases are a class of extended-spectrum β-lactamases that can hydrolyze penicillins, first to third generation cephalosporins, and monocyclic antibiotics and have their activities inhibited by extended-spectrum β-lactamase inhibitors (e.g., clavulanic acid, sulbactam), etc. At present, the most reported extended-spectrum β-lactamases are CTX-M-type enzymes (which are divided into five major classes). The most widely reported extended-spectrum β-lactamases are CTX-M-type enzymes (which can be categorized into five major groups: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25)(Seo & Lee, 2021).

Finally, with the emergence of multidrug-resistant strains, some highly effective antibiotics have become “antibiotics of last resort”, with polymyxin E considered to be the last line of defense against multidrug-resistant and carbapenem-resistant Gram-negative bacteria, but in recent years there have been an increasing number of reports of colistin (polymyxin E) resistant bacteria(Hussein et al., 2021). Liu YY et al. revealed by whole plasmid sequencing that polymyxin E resistance may be caused by the plasmid-mediated mcr-1 gene(Liu et al., 2016). Liu YY et al. revealed by whole plasmid sequencing that colistin resistance may be caused by the plasmid-mediated mcr-1 gene(Dadashi et al., 2022). Tigecycline and colistin are the last antibiotics against carbapenem-resistant bacteria, and it was found that a plasmid encoding the colistin resistance gene, mcr-1, and the tigecycline-resistance enzyme, tet(X6), existed in the same strain of *E. coli*, and that the presence of the two plasmids made *E. coli* co-resistant to these two classes of antibiotics(Xu et al., 2021b). Researchers predicted that the emergence of plasmids co-integrating mcr-1 and tet(X4) would pose a significant threat to humans, Lu X et al. obtained seven evolutionary plasmids carrying mcr-1 and tet(X4) in vitro and further demonstrated that the plasmids could be inherited(Lu et al., 2021). Shafiq M et al. Detection of a broadly resistant *E. coli* isolate co-carrying plasmid-mediated blaNDM-5 and tet(X4)

genes(Shafiq et al., 2022).

Horizontal gene transfer-mediated drug resistance

Tigecycline is used as a broad-spectrum glycylcycline antibiotic for the treatment of *E. coli* infections, but tigecycline-resistant strains have emerged clinically. The mechanism of resistance involves flavin-dependent monooxygenase (tetX), and studies have shown that the emergence of tetX can increase resistance to tigecycline(Li et al., 2016). The main resistance mechanism is that tet(X3/X4) can directly inactivate tigecycline potency through hydroxylation of carbon 11a(Cui et al., 2020)。As tet(X3/X4) is present on mobile plasmids, this leads to horizontal transfer of resistance across strains and species. Studies suggest that high levels of plasmid-mediated tigecycline resistance genes tet(X3) and tet(X4) emerged in 2019, which poses a significant threat to global public health(Li et al., 2023).

It was shown that splicing plasmid-mediated horizontal gene transfer is the main mechanism mediating the spread of antibiotic resistance genes in *E. coli*(Mota-Bravo et al., 2023). Minja CA et al. showed that out of 51 blaCTX-M-15 positive donor isolates, 45 transferred the plasmid via splicing(Minja et al., 2021). It has been shown that *E. coli* performs horizontal gene transfer mainly through DNA released by cell lysis, and that it can transfer DNA to different bacteria by secreting vesicles loaded with plasmid DNA into the environment(Cooper et al., 2017; Maeusli et al., 2020).

Drug resistance in E. coli mediated by efflux pumps

As early as the 1990s, the drug-resistant nodular differentiation family (RND) was identified in *E. coli* and is represented by the AcrAB-TolC pump in *E. coli* (Fig. 5), which mediates bacterial multidrug resistance.The RND is located in the inner membrane, and as a transporter protein it has to interact with periplasmic articulation proteins and the outer membrane channel to excrete drugs directly across the inner, periplasmic, and outer membranes into the External(Li et al., 2015).

In the presence of *E. coli* AcrAB-TolC, drug efflux through the cell membrane forms an effective permeability barrier due to the presence of low-permeability pore proteins (i.e., “slow pore proteins”), which are capable of generating multidrug resistance(Li et al., 2015). It was shown that *E. coli* AcrAB-TolC is regulated by the multiple antibiotic resistance manipulator Mar, which is expressed as two separate transcriptional units, one of which is MarRAB, controlled by MarO, which specifies a Mar deterrent (MarR), an activator (MarA) and a small protein (MarB), who are respectively encoded by marR, marA and marB, with MarB located downstream of MarA(Alekshun & Levy, 1999; Weston et al., 2018). Under normal conditions, MarR represses the MarRAB manipulator by binding to the two palindromic sequences of marO, but when antibiotics are encountered, repression of MarR is disrupted and transcription of marRAB occurs.It has been shown that de-repression of the Mar manipulator results in the expression of MarA: each regulator promoter has a binding site called a ” marbox” binding site, MarA undergoes positive feedback when it binds to DNA sequences upstream of the marbox, the

repressor site of MarR, so this represses marR and allows marA to be activated. MarA expression promotes the activation of several genes in its regulator, including the AcrAB and TolC genes, which increases drug efflux and lead to multidrug resistance(Martin et al., 1999; Weston et al., 2018). It was shown that drug resistance aspects were affected in strains lacking the gene encoding the AcrAB-TolC multidrug efflux pump (ΔtolC or ΔacrB)(Kobylka et al., 2020).

Mechanisms Of antibiotic Resistance In E. faecalis

Drug resistance mediated by mutations in drug resistance genes

There are two mechanisms of resistance to β-lactam antibiotics in *Enterococcus faecalis* (*E. faecalis*): the production of β-lactamases and the alteration of the affinity of penicillin-binding proteins for β-lactam antibiotics or the overproduction of specific penicillin-binding proteins, which, according to the study, are mediated by β-lactamases in *E. faecalis*(Ono et al., 2005). Studies have shown that resistance to β-lactam antibiotics in *E. faecalis* can be mediated by the production of a non-inducible β-lactamase(Herrera-Hidalgo et al., 2023). The presence of penicillin-binding protein 4 (PBP4) in *E. faecalis* results in a low affinity for β-lactam antibiotics, which leads to a certain degree of resistance to β-lactam antibiotics in *E. faecalis*(Urban-Chmiel et al., 2022)，and PBP4 is considered to be the key molecular basis for the resistance of *E. faecalis* to β-lactam antibiotics(Lazzaro et al., 2021). Epidemiologic data suggest that the progressive increase in resistance to β-lactam antibiotics in *E. faecalis* is attributable to overexpression of PBP4(Lazzaro et al., 2021). PBP4 belongs to the class of transpeptidases involved in the formation of the peptidoglycan layer; whereas β-lactam antibiotics block peptidoglycan biosynthesis via PBP4 acylation(Moon et al., 2018; Timmler et al., 2022). Further studies revealed that PBP4-mediated resistance to β-lactam antibiotics in *E. faecalis* was associated with the CroRS two-component signaling system (TCS)(Kellogg et al., 2017). Timmler SB et al. showed a correlation between PBP4 and the CroR system(Timmler et al., 2022)，the exact mechanism of which requires further experimental confirmation.

Vancomycin is commonly used for severe drug-resistant Gram-positive bacterial infections(2012a)，and plays a twofold role in the adjuvant treatment of colorectal cancer: on the one hand, vancomycin depletes butyrate-producing bacteria in the gut, thereby enhancing the efficacy of radiotherapy; on the other hand, it inhibits the bacteria that convert primary bile acids into secondary bile acids, thereby enhancing the efficacy of anticancer therapy(Singh et al., 2020; Yang et al., 2023). Since the first discovery of vancomycin-resistant *E. faecalis* clone sequence type 796 (ST796) in Australia in 2011, drug-resistant strains are now widely reported worldwide(Li et al., 2022). A total of nine vancomycin resistance cluster genes of the Van family have been identified, with VanA and VanB being the most common among clinical isolates(Raza et al., 2018; Zalipour et al., 2019). Taji A et al. showed that vanA gene was detected in 37.7% of *E. faecalis* isolates(Taji et al., 2019). Strateva T et al. tested and characterized an isolated strain of *E. faecalis* and found that the vanA gene cluster was on a segregating overlapping cluster with two repetitive IS1216E sequences around its flanks, followed by splicing experiments by filtered

mating assay using *E. faecalis* JH2-2 as a receptor strain, which showed unsuccessful results in terms of transferring vancomycin resistance, suggesting that the The possible location of the vanA gene cluster at the chromosomal position(Strateva et al., 2019). According to the study, the Tn1549 transposon carries the vanB manipulator on it(Simar et al., 2023). Although there are fewer reports on VanB, it has attracted much attention from scholars because of its high detection rate(Sadowy, 2021).

The main mechanism of resistance to linezolid in enterococci involves the G2576T mutation in the 23S rRNA gene(Rodríguez-Noriega et al., 2020)，and other mechanisms are mutations in the L3 and L4 ribosomal proteins as well as in two plasmid vector genes (cfr and optrA)(Arias & Murray, 2012). According to research, optRA is located in a new gene cluster containing the chloramphenicol output gene fexA. The protein product of optRA belongs to the ATP binding cassette (ABC) - F protein superfamily, and its resistance is mediated by ribosome protection. Compared with other gene determinants such as cfr or 23S rRNA and ribosomal protein mutations, mutations in optrA are a common cause of oxazolidinone resistance in *E. faecalis*(Roy et al., 2020). The research results of Deshpande LM et al. showed that isolates with chromosome localization of optrA exhibited different array structures. The flank regions of the optrA arrays of *E. faecalis* from Thailand and isolates from France were different. From the results of gene array analysis, it can be seen that with the continuous spread of optrA, a large degree of gene rearrangement is occurring, and the core genetic elements remain similar. However, in isolates from different geographical locations, their positions in the array are not the same(Deshpande et al., 2018). Therefore, the monitoring of the flanking regions of the optrA array is of great clinical importance.

Horizontal gene transfer-mediated drug resistance

The genome of *E. faecalis* was found to be highly plastic, and resistance to other antibiotics, such as high levels of aminoglycoside resistance, high levels of ampicillin resistance, and vancomycin resistance, is readily acquired through mutations in resistance genes or through horizontal transfer of genetic elements conferring resistance determinants(García-Solache & Rice, 2019). It was confirmed that transposons constitute the majority of the mobile genetic elements present in the genome of *E. faecalis*, and that Tn916, as the first confirmed splice transposon, carries tetracycline resistance and is able to be transferred to the chromosome of the recipient cell or to a splice plasmid by transposition, and that transposon incorporation into the splice plasmid increases the frequency of transfer(García-Solache & Rice, 2019).

Data from the China Antimicrobial Drug Surveillance Network (CDSN) showed that the high-level gentamicin resistance rate in *E. faecalis* ranged from 28.8% to 61.4% from 2005 to 2017, and was mainly mediated by the bifunctional enzyme encoded by the fused aac(6')-aph(2") gene in *E. faecalis*, 6'-acetyltransferase-2"-phosphotransferase(Ferretti et al., 1986). The aac(6')-

aph(2") gene is plasmid-borne in most cases and is located on the *E. faecalis* Tn5281-like transposon(Zhang et al., 2018). The non-truncated form of Tn5281 consists of a central region containing the aac(6')-aph(2") gene flanked by inserted inverted repeats of sequence IS256, whereas the truncated form is the aac(6')-aph(2") 3'- or 5'-end, or both lacking IS256(Zhang et al., 2018). Daikos GL et al. showed that 24 out of 30 isolates containing the truncated form transferred gentamicin resistance, while only 3 out of 34 isolates containing the nontruncated form transferred gentamicin resistance, suggesting that the truncated variant is mobile and more effective in transferring gentamicin resistance(Daikos et al., 2003).

It has been shown that the bacterial type IV secretion systems (T4SSs) are a functionally diverse translocation superfamily, and that one of its major functional subfamilies is the splicing system that mediates DNA transfer between bacteria, and that the splicing system can propagate removable genetic elements that typically encode bacterial resistance to antibiotics(Costa et al., 2021). The transferable plasmids of multidrug-resistant *E. faecalis* are T4SS with a functional plasmid-encoded (PE-T4SS) and a chromosome-encoded T4SS (CE-T4SS); compared with PE-T4SS, CE-T4SS exhibits different characteristics in protein structure and can mediate large genome-wide gene transfer(Hua et al., 2022). The study by Hua M et al. identified a widely distributed CE-T4SS in *E. faecalis*, and to better understand the process of gene transfer, the researchers analyzed the oriT element(Hua et al., 2022). At the initiation site of horizontal gene transfer, the researchers identified four putative orit with reverse complementary structural domains, orit1-orit4, and hypothesized experimentally that oriT4 is the required initiation site for horizontal gene transfer mediated by CE-T4SS in D5165. The investigators selected CE-T4SS+ reference strain ATCC 19433 as a donor and a popular erythromycin-resistant ST179 strain, S6008, as a recipient, suggesting that CE-T4SS induces gene transfer in the host(Hua et al., 2022).

Multidrug efflux system-mediated drug resistance

EfrAB, a heterodimeric multidrug ATP-binding cassette (ABC efflux system family) transporter protein, causes endogenous resistance to antibiotics including fluoroquinolones in Enterococcus spp.(Shiadeh et al., 2020). Shiadeh SMJ et al. All ciprofloxacin-resistant *E. faecalis* isolates showed varying degrees of overexpression of efrA and efrB genes(Shiadeh et al., 2020). A study by Esfahani S et al. found no significant relationship between the upregulation of the expression of the efflux pump and the level of minimal inhibitory concentration, and the researchers found isolates without any mutations in the expression of efflux genes but with drug resistance, and furthermore, 23 homologs of the ABC family of transporter proteins were detected in *E. faecalis* isolates(Esfahani et al., 2020). The above evidence suggests that the development of fluoroquinolone resistance may be the result of ABC family transporter proteins but not necessarily EfrA or EfrB.

Tetracycline is one of the most commonly used broad-spectrum antibiotics, and many bacteria have developed resistance to this antibiotic, the most common mechanism involves membrane-associated proteins (TetA), which exclude the antibiotic from the bacterial cell before inhibiting peptide elongation(Ramos et al., 2005). According to research reports, tetracycline

repressor protein (TetR) family proteins affect the tolerance of *E. faecalis* to tetracycline by controlling the expression of tetracycline efflux pump genes, such as the regulation of efflux pumps by the TetA gene(Gu et al., 2020). TetR proteins control the expression of the tet gene, the product of which confers bacterial resistance to tetracycline(Ramos et al., 2005). Research has shown that tetR and tetA are adjacent and oriented differently, and their gene products tightly control the expression of tetA and tetR(Ramos et al., 2005), TetR homodimers block the promoter of efflux pump genes by binding to repeat palindromic sequences in the upstream gene intergenic region using helix α1 to α3. In the presence of tetracycline, TetR homodimers interact with tetracycline and magnesium to form protein ligand complexes, which cause conformational changes in the TetR ligand complex, leading to the release of TetR homodimers from the promoter of efflux pump genes. This separation activates the expression of tetracycline related efflux pumps and squeezes tetracycline out of bacterial cells(Gu et al., 2020).

COMMONALITIES AND DIFFERENCES IN DRUG RESISTANCE

Consistency of Resistance Mechanisms of the Same Bacteria to Different Types of Antibiotics

Studies have shown that the same bacteria can be resistant to multiple antibiotics at the same time; are the resistance mechanisms similar? The resistance mechanisms of *B. fragilis* to carbapenems, tetracyclines and metronidazole are all mediated by efflux pumps(Ghotaslou et al., 2018a; Yekani et al., 2022); the resistance of *F. nucleatum* to β-lactam antibiotics and chloramphenicol is mediated by the class D β-lactamase FUS-1(Dupin et al., 2015)and the acetyltransferase (CAT)(de Souza Filho et al., 2012), respectively, and the associated proteases are the common mechanisms of resistance in this group of bacteria. The resistance of *E. coli* to rifampicin and β-lactam antibiotics is due to mutations in the rpoB and ampC genes, respectively(Kakoullis et al., 2021), it can be seen that mutations in resistance genes are the main resistance mechanism of *E. coli*; In previous studies, *E. faecalis* has developed varying degrees of resistance to β-lactam antibiotics, linezolid, and vancomycin. The resistance mechanisms are attributed to overexpression of the β-lactam antibiotic binding protein PBP4(Lazzaro et al., 2021), the G2576T mutation in the 23S rRNA gene and mutations in the L3 and L4 ribosomal proteins as well as in two plasmid-borne genes (cfr and optrA)(Rodríguez-Noriega et al., 2020), and the vanA gene cluster located at chromosomal location in *E. faecalis* mediated vancomycin resistance(Strateva et al., 2019), which shows that resistance gene mutations are a common resistance mechanism in *E. faecalis* during the development of resistance to different antibiotics.

Different Bacteria Have Different Resistance Mechanisms To The Same Antibiotics

Are there similarities in the resistance mechanisms of different bacteria facing the same antibiotic? Both *E. coli* and *B. fragilis* are resistant to carbapenem antibiotics, and *E. coli* resistance to carbapenem antibiotics is due to carbapenemase production(Nordmann et al., 2011); whereas *B. fragilis* resistance to carbapenem antibiotics is mainly due to increased expression of

efflux pumps(Yekani et al., 2022). The increase in drug resistance of *B. fragilis* is mainly due to the horizontal transfer of tetracycline resistance genes(Boiten et al., 2023)； whereas, for *E. coli*, flavin-dependent monooxygenase (tetX) leads to an increase in tigecycline resistance(Li et al., 2016)； thus, it can be seen that *B. fragilis* and *E. coli* have a certain degree of resistance to either tigecycline or tetracycline, but are not the same in terms of the mechanism of resistance.

SUMMARY AND OUTLOOK

Colorectal cancer has been one of the threats to human health in the past time, and the intestinal microbiota has acted as an important environmental factor influencing the occurrence and development of colorectal cancer in recent years. Certain microorganisms in the human gut microbiota are pathogenic microorganisms that contribute to the development and progression of colorectal cancer, such as *B. fragilis*, *F. nucleatum*, pathogenic *E. coli*, and *E. faecalis*. Clinical administration of antibiotics is the most common approach for the treatment of these bacteria, but with the prolonged use of a particular antibiotic or the evolution of pathogenic microorganisms, resistance has emerged in reports of colorectal cancer-associated flora from all over the globe, and it can be seen that the emergence of drug-resistant flora does not seem to be accidental, but rather systematic. The isolates of drug-resistant strains of colorectal cancer-associated flora as well as the detection rate of drug-resistant genes are also described in this review.

In this review we describe the content of *B. fragilis*, *F. nucleatum*, *E. coli* and *E. faecalis* associated with colorectal cancer and the antibiotic use associated with them; antibiotic-resistant isolates found in various parts of the globe as well as detection of resistance genes, it can be seen that *B. fragilis* as well as *F. nucleatum* are highly resistant to metronidazole and carbapenem antibiotics, among them, *B. fragilis* is more commonly used in clinical practice with metronidazole, so most of the detected resistant isolates are related to metronidazole resistance, *F. nucleatum* has a higher resistance rate to erythromycin, while research reports show that *E. coli* has developed varying degrees of resistance to many antibiotics, *E. faecalis* has high resistance to clindamycin in lincosamide antibiotics, and these four bacteria have varying degrees of resistance to β-lactam antibiotics. Therefore, these types of colorectal cancer-related microbiota are widely present around the world, and their inherent or environmental resistance cannot be ignored. It is necessary to fully understand their resistance characteristics and provide more effective prevention and treatment strategies.

Secondly, in this review, we describe in detail the unique resistance mechanisms of *B. fragilis*, *F. nucleatum*, *E. coli*, and *E. faecalis*, including the resistance mechanisms associated with β-lactam antibiotics, horizontal gene transfer, changes in the expression of active efflux mechanisms, and changes in the expression of their unique resistance genes. It can be seen that the four species of bacteria in the resistance mechanism have different mechanisms of expression, but in general, the effect of drugs on bacteria and bring resistance is not simply a "behavior", nor is it simply caused by a gene change, but rather a systematic and complex linkage changes, some of the specific changes in the mechanism of the change has not been

thoroughly studied until now. Some of the specific mechanisms of change have not been fully investigated, but based on our summary of the unique resistance mechanisms of several bacteria, it is possible to better utilize and manage such antimicrobials. Among the mechanisms of resistance that we have not described in detail, there are also many that are highly instructive for the clinical use of antimicrobials, which will increase the chances of treating and preventing colorectal cancer, and better management of antibiotic exposure and disease prevention in the environment will undoubtedly reduce the global spread of these resistant bacteria, which will have far-reaching implications for human health and survival.

Finally, we conducted a deeper exploration of the relationship between bacteria and antibiotics based on the resistance mechanisms of the four bacteria reported in the research. We discussed whether the resistance mechanisms of different bacteria to the same antibiotic are the same. Firstly, we found that the four bacteria associated with colorectal cancer have the same resistance mechanisms to the same antibiotic, indicating that antibiotics have developed the same resistance in multiple bacteria. We should start from the innovation of antibiotics themselves, such as clinical combination therapy of β-lactam antibiotics and β-lactam enzyme inhibitors, to enhance the efficacy of antibiotics; Secondly, it was found that there are different resistance mechanisms to the same antibiotic between B. fragile and *E. coli* associated with colorectal cancer. This may be related to the antibacterial mechanism of antibiotics against bacteria. Therefore, starting from the bacteria themselves, antibiotics can be used to target a certain structure of the bacteria, such as the cell wall or membrane, and relevant drugs can be used to enhance the antibacterial effect. We also explored from the perspective of the same type of bacteria that exhibit the same resistance mechanism when facing different antibiotics. This phenomenon was observed in all four bacteria associated with colorectal cancer, indicating that bacteria have a universal resistance mechanism to different types of antibiotics. This may lead to the bacteria developing the ability to resist antibiotics in certain aspects, which may result in the widespread spread of resistant strains and high drug resistance. At present, there is a trend of increasing drug resistance in the gut microbiota associated with colorectal cancer. In order to better treat this life-threatening disease, significant changes should be made in the field of microbiology. Modern medicine should focus on targeted antibiotic development or combination therapy for bacteria in the research and improvement of antibacterial drugs, making efforts to protect human health.

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Yu Gan conceived and designed the manuscript, analyzed the data, prepared the figures and tables, wrote or reviewed a draft of the article, and approved the final version.
- Hao Yang conceived and designed the manuscript, reviewed drafts of the article, and approved the final version.
- Maijian Wang conceived and designed the manuscript, reviewed the figures and tables, and approved the final version.
- Jida Li conceived and designed the manuscript, drew and reviewed the figures and tables, wrote and reviewed the draft article, and approved the final version.

Data Availability

The following information was supplied regarding data availability: This is a literature review; there is no raw data.

The Audience it is Intended for

The audience it is intended for researchers in related fields such as gastrointestinal diseases, intestinal flora, and colorectal cancer, etc.

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Figure 1

Changes in global colorectal cancer incidence and deaths, 2017-2022

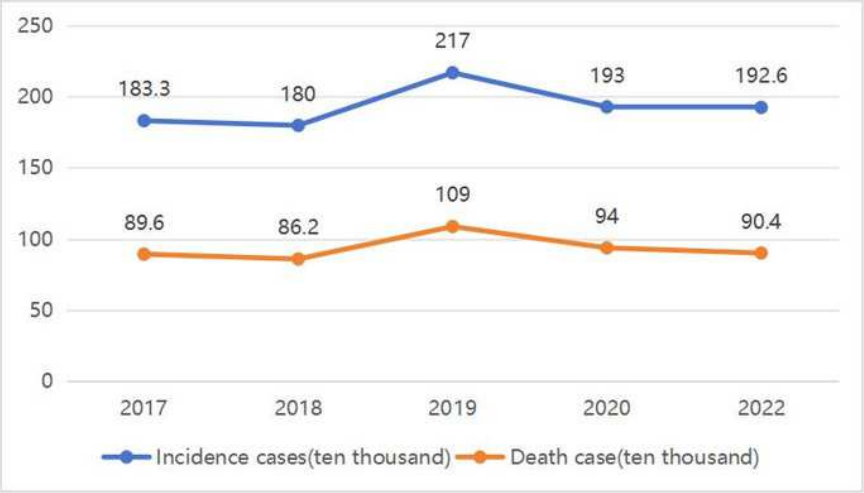

Figure. 1: Changes in global colorectal cancer incidence and deaths, 2017-2022(Bray et al., 2018; Fitzmaurice et al., 2019; Kocarnik et al., 2022; Sung et al., 2021)

Figure 2

Literature reports of intestinal flora associated with colorectal cancer in the last decade

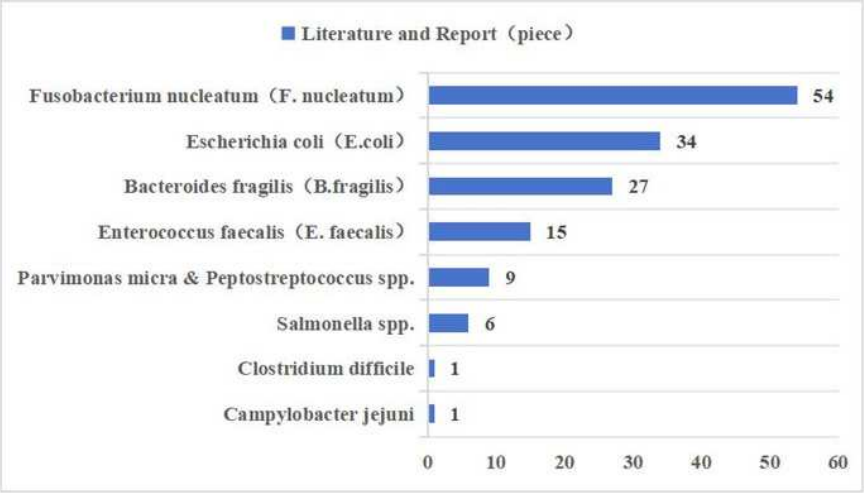

Figure. 2: Literature reports of intestinal flora associated with colorectal cancer in the last decade(Dougherty & Jobin, 2023; Song et al., 2020)

Figure 3

Timeline of antibiotic development

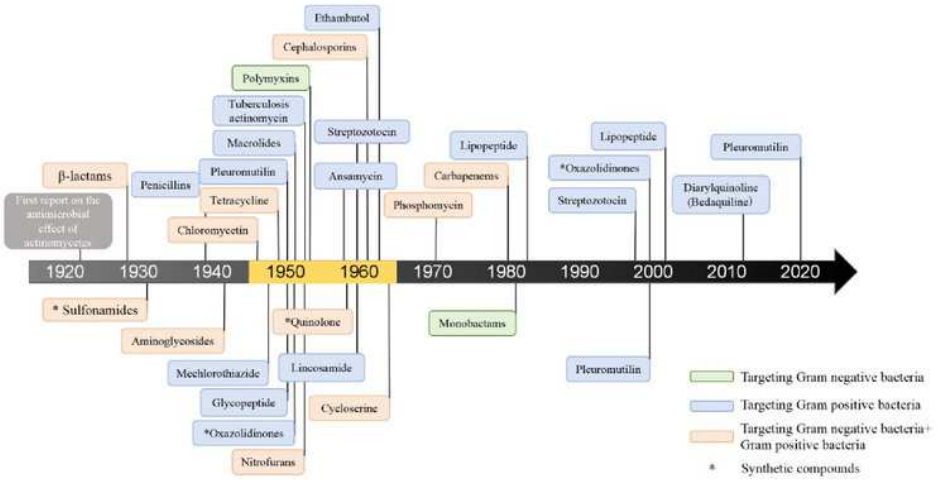

Figure. 3: Timeline of antibiotic development (Hutchings et al., 2019; Lewis, 2020)

Figure 4

Mechanisms of horizontal gene transfer-mediated drug resistance

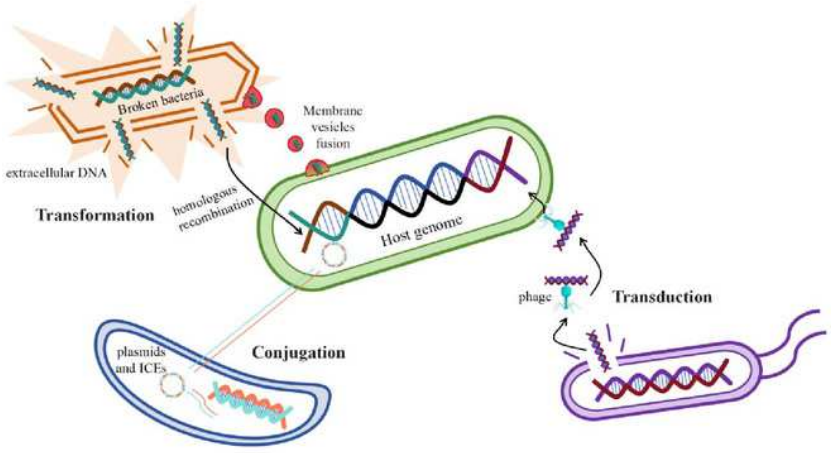

Figure. 4: Mechanisms of horizontal gene transfer-mediated drug resistance

Figure 5

Mechanism of *E. coli* AcrAB-TolC-mediated efflux

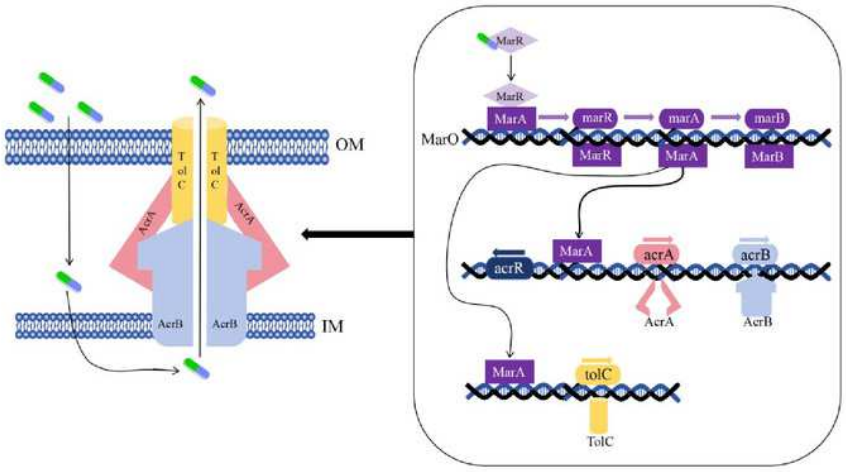

Figure. 5: Mechanism of *E. coli* AcrAB-TolC-mediated efflux

Table 1(on next page)

Resistance profiles and resistance mechanisms of four colorectal cancer-associated enteric bacteria

Table 1:

Resistance profiles and resistance mechanisms of four colorectal cancer-associated enteric bacteria

Bacteria	Drug class	Major drug resistance genes	Resistance mechanisms	References
enterotoxigenic *Bacteroides fragilis*	Carbapenems	*cfiA*	The upstream region of the *cfiA* gene undergoes mutations through insertion sequences (ISs) elements, as ISs induce transcription of *cfiA*.	(Alauzet et al., 2019)
	Metronidazole	*nim*	*nim*A-positive strains mainly reduce 5-Ni to its amine derivatives, thus avoiding the formation of nitroso groups .	(Edwards & Read, 2000; Yekani et al., 2022)
	Tetracycline	*tetQ*、*tetX*	The *tetX* gene encodes an oxidoreductase that inactivates tetracycline under aerobic conditions.	(Bartha et al., 2011)

Table 1. (Contd.)

Bacteria	Drug class	Major drug resistance genes	Resistance mechanisms	References
	Clindamycin	*ermB*、*ermF*、*mefA*	erm genetically determined macrolide lincosamide streptavidin-type methylase, which alters the ribosome and prevents clindamycin from binding efficiently to the ribosome.	(Johnsen et al., 2017; Kierzkowska et al., 2019)
	Lincomycin	*linA*	*linA* is an O-nucleotide transferase located in NBU2, which is mainly mobilized into the *B. fragilis* receptor by proteins encoded on coupled transposons, leading to drug resistance.	(Eitel et al., 2013; Wang et al., 2000)
Fusobacterium nucleatum	β-lactams	*blaFUS-1*	*blaFUS-1* hydrolyzes substrates through the formation of acylases from the active-site serine.	(Bush & Jacoby, 2010; Voha et al., 2006)
pathogenic *Escherichia coli* (*E.coli*)	β-lactams	*CTX-M*	Can encode ultra-broad-spectrum β-lactamases, which show resistance to β-lactam antibiotics through hydrolysis.	(Hussain et al., 2021; Naselli et al., 2022)

11 **Table 1.** (Contd.)

Bacteria	Drug class	Major drug resistance genes	Resistance mechanisms	References
	Rifampicin	*rpoB*	Rifampicin binds to the beta subunit of RNA polymerase to inhibit transcription, while substitution in *rpoB* inhibits rifampicin binding.	(Goldstein, 2014; Patel et al., 2023)
		ampC	Firstly, the basic *ampC* β-lactase is produced, and then the antibiotic accumulates cell wall degradation products and competes with UDP-N-acetylpeptide for binding to AmpR. As the binding of UDP-N-acetylpeptide to AmpR decreases, AmpR undergoes conformational changes, leading to an increase in *ampC* production.	(Tamma et al., 2019)
	Tetracyclines (Tigecycline)	*tet(X)*	Covalent inactivation of all tetracyclines is achieved by the addition of hydroxyl groups at position C-11a, located between the C and B rings of the tetracycline core.	(Grossman, 2016)

13 **Table 1.** (Contd.)

Bacteria	Drug class	Major drug resistance genes	Resistance mechanisms	References
	PolymyxinE	*mcr-1*	The *mcr-1* gene encodes a phosphoethanolamine transferase, which is responsible for modifying the lipid A portion of LPS by the addition of phosphoethanolamine, thereby decreasing its binding affinity for mucin.	(Barlaam et al., 2019)
Enterococcus faecalis	β-lactams	*pbp4*	Reduced affinity of penicillin for *pbp4* occurs through the production of β-lactamases that can hydrolyze and inactivate the drug or because of point mutations in the penicillin-binding domain.	(Conceição et al., 2014; Hiraga et al., 2008)
	Oxazolidinones (Linezolid)	*optrA*	The *optrA* gene encodes the ABC-F protein, which generates resistance through ribosomal protection, specifically, active translocation of the antibiotic from its ribosomal target site.	(He et al., 2016; Schwarz et al., 2021)

15 **Table 1.** (Contd.)

Bacteria	Drug class	Major drug resistance genes	Resistance mechanisms	References
	Tigecycline	*tetM*, *tetO*, *tetS*	Competitively binds to bacterial ribosomes and interferes with tetracycline-ribosome binding. Confers resistance by ribosome protection (RP).	(Huys et al., 2004)

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