Review

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# *Bacteroides* mobilizable and conjugative genetic elements: antibiotic resistance among clinical isolates

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## ABSTRACT

The conjugation is one of the most important mechanisms of horizontal gene transfer in prokaryotes, leading to genetic variation within a species and the acquisition of new traits, such as antibiotic resistance. *Bacteroides* is an obligate anaerobe of the colon and a significant opportunistic pathogen. Antibiotic resistance among *Bacteroides* spp. is rapidly increasing, largely due to the dissemination of DNA transfer factors (plasmids and transposons) harbored by members of this genus. Transfer factors can be divided into two classes, conjugative and mobilizable.

Species of the intestinal *Bacteroides* have yielded different resistance plasmids, all of which have been intensely studied, the plasmids encode high-level MLS resistance conferred by a conserved *erm* gene.

It has been reported an interesting observation associated with the transfer of several of these types of elements, all of which conferred $Tc^r$ and displayed greatly increased transfer efficiency following exposure to tetracycline. Many of the conjugative transposons (CTns) in *Bacteroides* are related to various genetic elements (such as CTnDOT, CTnERL, NBU and others). CTnDOT carries a tetracycline resistance gene, *tetQ*, and an erythromycin resistance gene, *ermF*.

Resistance to drugs used to treat *Bacteroides* infections, such as clindamycin, has also been increasing. These conjugal elements have been found in *Bacteroides* clinical isolates. Thus, horizontal gene transfer could conceivably have played a role in the rising incidence of resistance in this bacterial group.

**Keywords: antimicrobial resistance, *Bacteroides*, conjugative transposons**

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## Elementos genéticos conjugativos y mobilizables en *Bacteroides*: resistencia a los antibióticos en aislamientos clínicos

## RESUMEN

La conjugación es uno de los mecanismos más importantes de la transferencia horizontal de genes en procariotas, lo que lleva a la variación genética dentro de una especie y la adquisición de nuevos rasgos, como la resistencia a los antibióticos. *Bacteroides* es un anaerobio obligado y un patógeno oportunista importante. La resistencia a los antibióticos entre especies de *Bacteroides* está aumentando rápidamente, debido en gran parte a la difusión de los factores de transferencia de ADN (plásmidos y transposones) albergado por los miembros de este género. Los factores de transferencia se pueden dividir en dos clases, conjugativos y movilizables. Las especies de *Bacteroides* han presentado plásmidos de resistencia a los antibióticos, todos los cuales han sido intensamente estudiados. Estos plásmidos codifican de alto nivel de resistencia MLS conferida por un gen *erm* conservado. Se ha informado una observación interesante asociada a la transferencia de varios de estos tipos de elementos, todo lo cual confiere mayor resistencia y que aparecen en gran medida la eficiencia de transferencia después de la exposición a la tetraciclina. Muchos de los transposones conjugativos (CTn) en *Bacteroides* están relacionados con varios elementos genéticos (como CTnDOT, CnTnERL, NBU y otros). CTnDOT lleva un gen de resistencia a la tetraciclina, *tetQ*, y un gen de resistencia a la eritromicina, *ermF*. La resistencia a los medicamentos utilizados para tratar infecciones por *Bacteroides*, tales como la clindamicina, también ha ido en aumento. Estos elementos conjugativos han sido encontrados en los aislados clínicos de *Bacteroides*. Por lo tanto, la transferencia horizontal de genes posiblemente podría jugar un papel importante en la creciente incidencia de la resistencia bacteriana en este grupo.

**Palabras clave: resistencia antimicrobiana, *Bacteroides*, transposones conjugativos**

## INTRODUCTION

Conjugal genetic exchange in *Bacteroides* was first described in 1979 when reports from three laboratories demonstrated conjugally transmissible macrolide-lincosamide-streptogramin (MLS) resistance in this genus. This resistance phenotype was important because it permitted bacterial growth in the presence of clinically effective and widely used antibiotic clindamycin. This resistance phenotype was similar to that seen in Gram-positive bacteria (e.g., streptococci, staphylococci and bacilli).

In these bacteria, the MLS gene (designated *erm*) encoded and RNA methylase that modified specific adenine residues in the 23S rRNA, thus preventing MLS drugs from binding to the ribosome and inhibiting protein synthesis. The genetic basis of such conjugal transfer has been traced to both plasmids as well a nonplasmid elements. The latter appear to reside chromosomally and to resemble the conjugative transposons of the Gram-positive bacteria in their behavior[1].

The conjugation is one of the most important mechanisms of horizontal gene transfer in prokaryotes, leading to genetic variation within a species and the acquisition of new traits, such as antibiotic resistance or the ability to produce toxins. *Bacteroides* conjugative transposons (CTn) were among the first transposons discovered, and they have since been shown to play a central role in the dissemination of antibiotic resistance genes in the related genera[2].

In particular, a family of CTns, exemplified by CTnDOT and CTnERL, appears to be playing an important role in transferring resistance genes among *Bacteroides* strains. CTns of this family not only transfer themselves but also mobilize coresident plasmids. In addition, proteins encoded on these CTns trigger *in trans* the excision and circularization of mobilizable integrated elements called NBUs, and they mobilize these circular forms *Bacteroides* or *Escherichia coli* recipients[3].

They may also mobilize other integrated elements that have been given transposon designation, such as Tn*4399*, Tn*4555*, Tn*5520*[4,5]. To distinguish mobilizable elements that have been given a transposon designation from nonmobilizable *Bacteroides* transposons such as Tn*4351* or Tn*4551*[6,7,8].

## BACTEROIDES TRANSPOSONS IN ANTIBIOTIC RESISTANCE PLASMIDS

Species of the intestinal *Bacteroides* have yielded three different resistance plasmids, all of which have been intensely studied: pBF4, a 41-kb plasmid from *B. fragilis*; pBFTM10, a 15-kb plasmid from *B. fragilis* (and its indistinguishable counterpart pCP1 from *B. thetaiotaomicron*); and pBI136, an 80 kb-plasmid from *B. ovatus* all share some common features (table 1). All three plasmids encode high-level MLS resistance conferred by a conserved *erm* gene[6,9,10].

The nucleotide sequence of two of the *erm* genes (*ermF* from pBF4 and *ermFS* from pBI136) has been determined, and the genes have been found to differ at only one nucleotide position. Physical analyses of both wild-type and mutant plasmids revealed the *erm* gene of each plasmid was bordered by a similar, if no identical, sequence, which flanked the gene in a directly repeated fashion. Other than their *erm* genes and the associated directly repeated DNA sequences, pBF4, pBFTM10 and pBI136 shared no detectable homology[11].

The repeated sequences bordering the *erm* genes of these three plasmids have been shown to be a related, if no identical, insertion sequence (IS) elements (IS*4400* on pBFTM10, IS*4351* on pBF4, and iso-IS*4351* on pBI136). These flanking IS elements form compound transposons with their associated *erm* genes, and genetic evidence for their transposition in both *B. fragilis* and *Escherichia coli*. In all three of these transposons the *erm* genes were juxtaposed to one copy of the IS element, suggesting some interaction between these two sequences. This suggestion has been experimentally explored by the analysis of the nucleotide sequence data, S1 nuclease transcription mapping studies, and the construction of gene fusions to evaluate promoter activity. Collectively, these data indicate that the *erm* genes arer under the transcriptional control of the promotors contained in the IS element[1,12,13].

Examples of the IS element being in opposite orientation with respect to the *erm* gene were found in the comparative examination of pBF4 and pBFTM10 with pBI136. Odelson *et al.*[10] have proposed a model to explain the formation of these transposons tha predicts that all three transposons evolved independently of one another. Following the entry of a similar *erm* gene into *Bacteroides*, transposition of the IS element next to the newly acquired gene resulted in the transcriptional control of *erm* by the IS element. This may have been required in the face of selective pressure because the invading *erm* gene could not be expressed in *Bacteroides* for several reasons (e.g., unrecognizable promoter, nofunctional upstream regulatory sequences on the *erm* mRNA)[10].

## A NEW NONPLASMID CONJUGATIVE ELEMENTS IN BACTEROIDES

It has been know since early in the 1980s that certain antibiotic-resistant strains of *Bacteroides fragilis* were capable of transferring their resistance without the involvement of detectable plasmid DNA. Such transfer elements have been placed in two categories with respect to antibiotic resistance phenotypes: those that transfer tetracycline resistance alone and those which transfer tetracycline and clindamycin resistances in a linked fashion[9].

Salyers and Shoemaker[12] reported an interesting observation associated with the transfer of several of these

**Table 1** **Summary of mobilizable and conjugative genetics elements that confers antimicrobial resistance in *Bacteroides*.**

| Genetic element | Description |
|---|---|
| pBF4, pBFTM10, pBI136 | 41-kb, 15-kb, 80-kb plasmids. They encode high-level MLS resistance conferred by *erm* genes |
| Tn*5030* | ERL-type element. Mobilizable transposon. That encodes tetracycline and MLS resistance |
| Tn*4399* | Transposon capable of mobilizing plasmids to E. coli recipient. |
| CTnDOT | Major conjugative transposon from *Bacteroides*. That carries *tetQ* and *ermF* genes |
| Tn*916* | Enterococcal CTnDOT-type elements found in *Bacteroides* isolates |
| NBU | Non-replicating *Bacteroides* units. NBUs, like the CTn that excise and mobilize them, excise to form covalently closed circular intermediates |
| Tn*5520*, Tn*4555* | Mobilizable transposons, they rely on the CnTn for transfer. This confers resistance to other antibiotics (such as β-lactamics) |
| CTnBST | Conjugative transposon. 100 kbp. This contains *ermB* gene |
| CTn*341* | CTn of the CTnDOT family. Major functional genes: DNA metabolism, conjugation and antibiotic resistance. |
| cLV25 | Movilizable transposon with similarity to the Tn*4399* |

types of elements, all of which conferred Tc$^r$ and displayed greatly increased transfer efficiency following exposure to tetracycline. Specifically, when these elements were transferred to *B. uniformis* and the resulting strain was exposed to inhibitory tetracycline, two circular DNA forms (10 and 11-kb) could be detected as extrachromosomal elements. Southern analyses indicated these circular molecules were normally integrated into the host cell chromosome. Certain of the Tc$^r$ nonplasmid elements examined by these authors did not mediate the excision of circular DNA forms.

Stevens et al.[13] have presented evidence suggesting that the control of production of these circular DNA forms resides in a region contained within the Tc$^r$ transfer element called ERL (confers Tc$^r$ and MLS resistance). Halula and Macrina[14] have also reported the partial cloning of Tc$^r$, MLSr element, called Tn*5030*, from *B. fragilis*. They estimated the size of this element to be in the 40 to 50-kb range, based on overlapping clones. Interpretation of their results was complicated by the unexpected finding that sequences related to Tn*5030* were present in the transconjugant strain from wich their genomic libraries were prepared. Further studies are needed to fully define the molecular structure of this element.

Tn*4399* was capable of mobilizing plasmids in intergeneric *Bacteroides* matings as well as in *Bacteroides-E. coli* matings (table 1). This transfer element provides yet another novel example of the genetic plasticity in anaerobic bacteria, and its is likely to play a role in the dissemination of antibiotic resistance determinants[2].

Other feature is the ability of most *Bacteroides* CTns to induce conjugation 1000- to 10000-fold in the presence of tetracycline. The transfer of both the CTn and unliked elements is enhaced by growth in the presence tetracycline at concentration of < 1 mg/L, and this induction is mediated by a complex signal transduction pathway that includes a two-component regulatory system (RteA and RteB) and at least one other regulatory protein, RteC[15]. The ability to mobilize other genetic elements and the antibiotic-stimulated transfer may in part explain the high tetracycline resistance and the high frequency of the other antibiotic resistance genes in *Bacteroides*[16].

## CTnDOT: A BACTEROIDES CONJUGATIVE TRANSPOSON

Many of the conjugative transposons (CTns) in *Bacteroides* are related to an element calle CTnDOT (table 1). CTnDOT carries a tetracycline resistance gene, *tetQ*, and an erythromycin resistance gene, *ermF*[16].

In fact, without tetracycline stimulation of donor cells, virtually no transfer occurs. Any studies identified a central regulatory region on CTnDOT that is required for tetracycline induction of transfer functions. This region contains a three-gene operon that consists of the tetracycline resistance gene *tetQ* and two regulatory genes, *rteA* and *rteB*.

RteA and RteB are most closely related to the sensor and response regulator components, respectively, of two-component regulatory systems. RteA presumably activates RteB, and activated RteB stimulates the expression of excision and transfer genes.

The regulatory cascade mediated by RteA, RteB and RteC is not, however, the first step in tetracycline stimulation of CTn transfer in *Bacteroides*. Expression of the *tetQ-rteA-rteB* operon itself is controlled by tetracycline. Stevens et al.[13] reported that fusion of *tetQ* to the reporter gene *uidA* produced fusion whose expression was stimulated by tetracycline.

Intercellular transposition of CTns in *Bacteroides* is thought to occur by the following steps. The CTn initiates conjugal transfer by excising from the chromosome to form a circular intermediate. This intermediate is nicked at the transfer origin (*oriT*), and a single-strand copy is transferred to the

recipient cell, recircularized, and integrated into the recipient´s genome[15,16].

Since CTnDOT appeared to integrate site selectively, the comparions of the sequences of the ends of CTnDOT with the sequences of the integration sites revealed some sequence similarity. One candidate for recognition sequence is a 10-bp sequence that is immediately adjacent to the site where CTnDOT entered the cromosome and at the right end of the circular form of the element. In the integrated form, this target 10-bp sequenced is 5-bp from the left end of CTnDOT from insertions in four other chromosomal sites. Similar 10-bp sequences were seen in all four cases[7,15,16].

The integration and excision of CTns have been studied in detail only in the case of Tn*916*, a CTn first found in enterococci. The CTnDOT-type elements differ in a number of ways from Tn*916*. First, Tn*916* integrates relatively randomly whereas CTnDOT appears to integrate site selectively into about seven sites on the *Bacteroides* chromosome. Second, there is no sequence similarity between CTnDOT and Tn*916* in any of the regions so far sequenced. A third difference between CTnDOT and Tn*916* is that transfer of CTnDOT is stimulated 1000- to 10000-fold by tetracycline, a fold increase much higher than the tetracycline stimulation reported for Tn*916* transfer[8].

The tetracycline-dependet stimulation of CTnDOT transfer is mediated by proteins encoded by three regulatory genes: *rteA*, *rteB* and *rteC*. No regulatory genes analogous to the *rte* genes of CTnDOT have been found on Tn*916*[16].

## REGULATION OF BACTEROIDES OPERON THAT CONTROLS EXCISION AND TRANSFER OF THE CTNDOT

Exist a translational attenuation-type regulation of the *tetQ-rteA-rteB* operon in response to tetracycline. RT-PCR analysis showed that similar amount of the mRNA from this operon is made regardless of whether tetracycline is present result rules out another possible model for attenuational control of gene expression, the binding of tetracycline to a structure in the mRNA itself in such a way as to cause antitermination.

In the case of an antitermination type of control, the concentration of *tetQ* mRNA should have been much higher under inducing conditions. Although *tetQ* mRNA was made both in the presence and absence of tetracycline stimulation, translation of the message, is much higher in tetracycline-stimulated cells than in cells no stimulated. This observation taken together with the fact that a translational fusion with *uidA* was responsible for much higher activity and a higher increase in tetracycline-stimulated cella than a transcriptional fusion in the same locus[8], supports the idea that regulation occurs at the level of translation rather than transcriptional.

Further evidence for translational attenuation came from mutagenesis experiments that were guided but the observation that hairpain structure could form in the leader region of the mRNA.

Production of RteA and RteB, the other protein encoded in the *tetQ-rteA-rteB* operon, should be regulated similarly to production of TetQ. That is, the proteins are produce at detectable levels only when the cells are stimulated with tetracycline. Since *rteA* and *rteB* have been shown to be in the same operon as *tetQ*, production of these proteins is presumably due to translational coupling one ribosomes begin to translate the operon mRNA. RteA and RteB have no role in tetracycline regulation of operon expression. This was somewhat surprising because RteA and RteB are both essential for CTn excision and transfer functions and resemble components of a two-component regulatory system. RteA, the putative sensor protein, is a sensing something other than tetracycline[15,16].

TetQ was not required for tetracycline stimulation, but its presence did have an effect. Moreover, increased levels of TetQ due increased levels copy numbers of *tetQ* caused a greater decrease in protein production. TetQ is a ribosome protection type of tetracycline resistance protein, which is most closely related to an elongation factor. TetQ modifies ribosomes so that tetracycline no longer binds as efficiently. The fact that a higher intracellular concentration of TetQ increased the MIC and further decreased the translation of operon mRNA suggets that one copy of *tetQ* is no sufficient to protect all of the ribosomes in the cell[8]. The modulating effect of TetQ on translation may be a means for the cell to limit the production of RteA and RteB and thus the amount of CTn excision and transfer that occurs. Excision of CTnDOT in *Bacteroides* is apparently not a lethal event because the chromosomal site from which the CTn is excised is resealed in the process[16], but too much activity of this sort could have some deleterious effect on fitness that could be important in an enviroment as competitive as the human colon.

### THE NBUs ELEMENTS

*Bacteroides* conjugative transposons can also mediate the excision and mobilization of unliked integrated elements called NBUs (non-replicating *Bacteroides* units). The NBUs so far characterized are 10 to 12 kbp in size. NBUs, like the conjugative transposons that excise and mobilize them, excise to form covalently closed circular intermediates that are transferred by conjugation to a recipient, where their integrate into recipient genome[17] (table 1).

The circular forms of the NBUs appeared not replicate and were designated nonreplicating units to distinguish them for the plasmids. The circular forms of the NBUs were see only when the strain was grown in medium containing tetracycline. Subsequently, we found that the NBUs are normally integrated in the chromosome and that *trans* action by a $Tc^r$ element is requerired to excise and circularize them[18].

The NBUs are sometimes cotransferred with $Tc^r$ elements, and it was postulated that the excised circular form of the NBUs were plasmidlike forms and were transferred like plasmids and the integrated into the recipient chrosomome[3,17].

The mobilizable element NBU2 (11 kbp) was found

originally in two *Bacteroides* clinical isolated, *B. fragilis* ERL and *B. thethaiotamicron* DOT. NBU[2] appeared to be very similar to NBU1 in a 2,5 kbp internal region, but this identify between NBU1 and NBU2 is limited to this small region. The sequence of NBU2 revealed two ORFs whose derived amino acid sequences were related to those of known antibiotic resistance genes previously found in Gram-positive bacteria. The deduced amino acid sequence of $linA_{N2}$, LinA(N2), had 50 to 52% identify and 70 to 72% similitary to the LinA´of *Staphylococcus aureus* and LinA on pIP855 in *S. haemolyticus*. LinA is an O-nucleotidyltransferase which inactives lincosamides including lincomycin and clindamycin. This is also the first sighting of a *linA* type gene in *Bacteroides* species[3,18].

## TN*4555* AND THE ANTIBIOTIC RESISTANCE IN *BACTEROIDES*

In *Bacteroides* species are integrated elements that are much smaller than the CTns. These elements, exemplified by NBU1, Tn*5520* and Tn*4555*, have been called mobilizable transposons because they rely on the CTns for transfer functions[8] (table 1).

The integrases of NBU1, Tn*5520* and Tn*4555* have been sequenced, and all are members of the lambda family integrases. NBU1 excision more closely resembles excision of phage lambda in that there is an *att* site formed by the joined ends that integrates into an identical site in the choromosome[5]. Although the mobilizable transposons rely absolutely on the CTns for transfer, there is so far no evidence for any significant sequence similarity between them and the CTns.

*Bacteroides* are potencial reservoirs of antibiotic resistance genes and Tn*4555* from *Bacteroides vulgatus* carries *cfxA*, encoding an extended spectrum ß-lactamase found in 80% of cefoxitin-resistant, imipenem-sensitive *Bacteroides* species tested[19].

Cefoxitin resistance was observed shortly after its introduction in the 1970s and elements such as Tn*4555* may be responsible for the rapid emergence of resistance. More recently, a ß-lactamase gene 98% identical to *cfxA* was found in 97% of amoxicillin-resistant *Prevotella* isolated from periodontitis patients20. Since there is potential for Tn*4555* and like elements to undermine the effectiveness of antibiotic treatment, it is important to understand all aspects of their dissemination.

The mobilizable transposon (MTn), Tn*4555* can be transferred (mobilized) to other bacteria when in the presence of CTn, a self-transmissible genetic element that moves from donor genome to recipient genome during cell to cell contact. Although transposons have been defined as mobile genetic elements that randomly insert into DNA by mechanisms not requiring homologous recombination, all know elements including MTns and CTns show some degree of target site selectivity[8].

CTns appear to have unique target site selection mechanisms which in some cases require homology between the CTn ends (*att*Tn) and the tartget. For example, CTnDOT targets a 10-bp sequence in the *Bacteroides* choromosome that has homology to its right end[15].

Tn*4555*, a clinically relevant MTn, carries all the genes necessary for its insertion into phylogenetically diverse hots. In the investigation of Bacic and Smith[4] all bacteria tested, there was preferred insertion site or target and while there were some shared motifs, none of these had ends. A lack of homology suggested that sequence alone was not the main determining factor for site selection, though the translated *Bacteroides* targets did have homology to BspA from *B. forsythus*. BspA is a cell-surface-associated, leucine-rich protein involved in adhesion to fibronectin and fibrinogen. BspA has repetitive amino acid sequences suggesting that repetitive areas in the DNA sequence are important for large, imperfect, direct repeats; however, there were no significant repeats in the other *Bacteroides* targets nor in the *E. coli* target, and the *E. coli* target was highly preferred with 90% of all insertions occurring there, more than for any of the others. Also the site of Tn*4555* insertion in the original clinical isolate *B. vulgatus* had no repeats nor did it have any amino acid homology to BspA[8].

The Mtn share a functional similarity to mobilizable plasmids in that they are not self-transmissible but rather they encode an element-specific mobilization gene(s) and a transfer origin, *oriT*, that utilize Tc$^r$-element conjugative apparatus to effect their transfer to a new host. These mobilization genes appear to be primarily responsible for DNA processing reactions in which they catalyze a strand-specific nick in the transposon at *oriT*[15].

Tn*4555* is a mobilizable transposon that carries the *cfxA* gene, which encodes a clinically significant, broad spectrum ß-lactamase responsible for widespread resistance to cefoxitin and other ß-lactams. Initial studies on Tn*4555* integration indicated that it proceeds by a site-specific recombination mechanism that utilizes a 6-bp crossover region in the target site[20]. Clearly Tn*4555* is not limited to one or two *Bacteroides* species or genera in the intestinal niche. There was no difference in excision from preferred sites versus non-preferred sites therefore these targets must benefit insertion[5,8].

Tn*4555* carries antibiotic resistance genes and these elements can be mobilized by a variety of genetic elements can be mobilized by a variety of genetic elements including large R-plasmids or by conjugal transposons such as the large *Bacteroides* Tc$^r$-elements[5]. However, unlike mobilizable plasmids, there transposons have minimal requerimets for stable maintenance in new hosts.

## OTHERS CONJUGATIVE TRANSPOSONS

Gupta et al.[21] used pulsed-field gel electrophoresis to show that the *B. uniformis* element carrying *ermB* was integrated into the chromosome and was thus probably a CTn (table 1). The CTn was named CTnBST. CTnBST was estimated to be about 100 kbp in size. A 13-kbp region containing *ermB* was

sequenced and compared to sequences then in the databases. The DNA sequence of the *ermB* gene was identical to genes found in *Clostridium difficile*. Outside the *ermB* gene, however, only a few hundred base pairs downstream of *ermB* had high sequence identity to DNA from gram-positive bacteria[22].

A *Bacteroides* CTn, CTnBST, integrates more site specifically than other well-studied CTns, CTnDOT and the enterococcal CTn Tn*916*. Moreover, the integrase of CTnBST, IntBST, had the C-terminal 6-amino-acid signature that is associated with the catalytic regions of members of the tyrosine recombinase family, most of which integrate site specifically (table 1). Also, in most of these integrases, all of the conserved amino acids are required for integration[23]. However, the IntBST had that changing three of the six conserved amino acids in the signature, one of which was the presumed catalytic tyrosine, resulted in a 1,000-fold decrease in integration frequency. Also, CTnBST differed from CTnDOT in that whereas the transfer frequency of CTnDOT is stimulated 100- to 1,000-fold by tetracycline, CTnBST exhibited constitutive transfer[24].

CTn*341*, originally found in a clinical isolate of *Bacteroides vulgatus*, is 52 kb in size and encodes genes for tetracycline resistance and regulation of transfer, conjugation, and DNA metabolism. The *mob* region of CTn341 is comprised of three genes, mobABC , as well as the transfer origin, *oriT*. The *oriT* region of CTn*341* has been located within 100 bp of *mobA* and the putative *nic* site was identified within this region. The Mob proteins are predicted to bind at this site and form the relaxosome complex which specifically nicks the DNA at the nick site prior to coupling it to the mating pore apparatus[25]. The *mob* gene expression is tightly regulated and transcription is induced by low levels of tetracycline through the two component regulatory system genes *rteA-rteB*.

CTn*341*, is a member of the most common CTn group, the CTnDOT family[26]. Sequence analysis revealed 46 genes and one functional group II intron (table 1). The genes fell roughly into three major functional groups: DNA metabolism, regulation and antibiotic resistance, and conjugation27. Mutational analyses of genes from each group were used to verify the proposed functional assignments. Based on G+C content and codon usage, the functional groups appeared to belong to different genetic lineages, indicating that CTn*341* is a composite, modular element. Comparisons with *Bacteroides* genome sequences suggested that the basic conjugation and excision genes are conserved in *Bacteroides* spp[27].

Other transfer factor is the cLV25. The cLV25 mobilization proteins have similarity to the Tn*4399* mobilization proteins and to mobilization proteins encoded by the CTnDOT *ermF* region. In addition, the genetic organization of the cLV25 mobilization genes and *oriT* is analogous to those of Tn*4399* and the CTnDOT *ermF* region[28] (table 1). Further, cLV25 can functionally crossreact with Tn*4399*. The cLV25 is a mobilizable transposon based on the presence of imperfect inverted repeats at its termini, an apparent target site repeat, and an open reading frame whose predicted protein has similarity to integrases[28].

## CONCLUSIONS

In general, *Bacteroides* are resistant to a wide variety of (recently many species have acquired resistance to erythromycin, clindamycin, and tetracycline). This high level of antibiotic resistance has prompted concerns that *Bacteroides* species may become a reservoir for resistance in other, more highly-pathogenic bacterial strains.

The conjugation is one of the most important mechanisms in the horizontal transfer of genes in prokaryotes, providing the capacity of variation between species by means of the obtaining of new genetic information.

To beginnings of the years 80s the scientific community demonstrated that certain clinical strains of *B. fragilis* resistant to the antibiotics were capable of transmitting this resistance by means of plasmids and without the presence of these. These elements establish two categories with regard to the resistance of antibiotics: the transfer of the resistance to tetracycline and the transfer of resistance to tetracycline and clindamycin together.

The CTn in *Bacteroides* that can manage to join to the chromosome or plasmids of the receptor bacteria. The potential of the CTn in *Bacteroides* due to the fact that they are capable of mobilizing plasmids co-residents in *trans* and in *cis*, and also of stimulating the excision and the transfer of integrated elements called units not replicate of *Bacteroides*.

The family of the CTn they are represented by CTnDOT and CTnERL, which increase the rates of conjugation in presence of 1 mg/L of tetracycline, which is very significant for that this antibiotic not only would select *Bacteroides*'s resistant strains if not that in addition would stimulate the transfer of genetic elements and of genes of resistance between bacteria y this situation could complicate the antimicrobial treatment in a several *Bacteroides* human infections.

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