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Review

Mobile genetic elements related to carbapenem resistance in *Acinetobacter baumannii*

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ABSTRACT

Acinetobacter baumannii is widely recognized as an important pathogen associated with nosocomial infections. The treatment of these infections is often difficult due to the acquisition of resistance genes. *A. baumannii* presents a high genetic plasticity which allows the accumulation of these resistance determinants leading to multidrug resistance. It is highlighted the importance of the horizontal transfer of resistance genes, through mobile genetic elements and its relationship with increased incidence of multidrug resistant *A. baumannii* in hospitals. Considering that resistance to carbapenems is very important from the clinical and epidemiological point of view, the aim of this article is to present an overview of the current knowledge about genetic elements related to carbapenem resistance in *A. baumannii* such as integrons, transposons, resistance islands and insertion sequences.

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Introduction

The *Acinetobacter baumannii-calcoaceticus* (Abc) complex has emerged as an important nosocomial pathogen. Among the members of this complex, *A. baumannii*, *A. pittii*, and *A. nosocomialis* are the three most common *Acinetobacter* species isolated in clinical settings.[1] *A. baumannii* has been extensively studied due to its association with infections of high mortality rates. *A. pittii* and *A. nosocomialis* are increasingly identified as causative agents of nosocomial infections.[2]

A. baumannii is considered an important nosocomial pathogen, causing a wide range of infections, including ventilator-associated pneumonia, bloodstream infections, urinary tract infections and meningitis. This species is naturally highly resistant to a number of antimicrobials commonly used in the clinical practice, such as first and second generation cephalosporins, aminopenicillins, and chloramphenicol.

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A. baumannii contains an intrinsic AmpC β-lactamase (bla_{ADC}) and OXA-51 serine-type oxacilinase (bla_{OXA-51}), which contribute to the natural resistance to β-lactams.[3] Moreover, this organism presents a great capacity to acquire new resistance mechanisms, including those responsible for carbapenem resistance.[4]

Carbapenem resistance in *A. baumannii* involves mainly the carbapenem-hydrolysing class D β-lactamases (CHDLs – Ambler class D) and less frequently, the metallo-β-lactamases (MBLs – Ambler class B). Carbapenem resistance may also be caused by other mechanisms such as, production of other carbapenemases, porin modification or loss, or by modification of the penicillin-binding proteins.[1,5]

Several acquired class D OXA-type β-lactamases have been identified as a source of carbapenem resistance in *A. baumannii*. Five main groups of CHDLs have been described in *A. baumannii*, corresponding to OXA-23-like, OXA-24/40-like, OXA-58-like, OXA-143-like and OXA-235-like enzymes.[6] OXA-23-like enzymes are the most widespread in *A. baumannii* worldwide and have been identified in all continents.[6]

In Brazil, OXA-23-like-producing *A. baumannii* is disseminated in many states and it is responsible for high endemic levels of multidrug-resistance.[7,8] The $bla_{OXA-143}$ gene has thus far been detected only in *A. baumannii* isolates from Brazil and is the second most frequent CHDL encoding gene.[9–11]

The $bla_{OXA-143}$ gene is frequently found in the Southeast region of Brazil, especially in the state of São Paulo. It is important to note that two new variants of this gene were recently described. The variants $bla_{OXA-235}$ and $bla_{OXA-231}$ were described in Minas Gerais and Paraná states, respectively.[12,13] This data demonstrates the detection of these new variants of $bla_{OXA-143}$ in Brazil is a cause of great concern and shows the potential of these new CHDLs to spread to other Brazilian regions.

Although $bla_{OXA-24/40-like}$ gene is disseminated in *A. baumannii* in Europe, in Brazil, this gene is still rare, with only a very few reports of a bla_{OXA-72} ($bla_{OXA-24/40-like}$ variant) in São Paulo,[9] Recife,[14] Porto Alegre and Curitiba.

Despite MBLs are less commonly identified in *A. baumannii* than the OXA-type carbapenemases, their hydrolytic activities to carbapenems are significantly more potent. Four MBLs have been identified in *A. baumannii*: IMP, VIM, SIM and, more recently, NDM.[15] It is important to note that MBL genes, such as NDM and IMP-1, have been described in *Acinetobacter* non-*baumannii* species, which demonstrates the capacity of these resistance genes to spread among different *Acinetobacter* species.[16,17]

Most of Ambler class A ESBLs possess activity against penicillins and broad-spectrum cephalosporins. However, specific GES variants have been shown to possess the ability to compromise the efficacy of carbapenems. Among *A. baumannii*, the variants GES-11 and GES-14 possess specific residues enlarging their hydrolysis spectrum (Table 1).[18,19]

The elevated genetic plasticity presented by *A. baumannii* has allowed the accumulation of many resistance determinants, which contributed to the high incidence of *A. baumannii* multirresistant to antibiotics. In this review, we present and discuss the characteristics of the different mobile genetic elements involved in the transfer of resistance determinants in *A. baumannii*.

AbaR-type genomic resistance islands

Genomic islands containing resistance markers are referred to as resistance islands. Resistance islands have been described mainly in Proteobacteria, including *Shigella flexneri*, *Salmonella enterica*, *Vibrio cholerae*, *Staphylococcus aureus*, and more recently, in *A. baumannii*.[20,21] *A. baumannii* isolates harbor large clusters of horizontally transferred genes conferring resistance to multiple antibiotics and heavy metals, which are integrated at a specific site in a particular ATPase gene.[22]

Fournier et al. described for the first time the *A. baumannii* Resistant Island (AbaR). AbaR is defined as a region which has transposed into a specific position in the chromosome, creating a 5 bp duplication site (ACCGC).[21] The backbone of AbaR is comprised of five open reading frames (ORFs) – *orf1*, *tniA*, *tniB*, *orf2*, *orf3* – which constitute the transposition module, and two other genes encoding to the universal stress protein (*uspA*) and a sulfate permease (*sul*).[21–23]

Several AbaR have already been described containing a variety of resistance genes, including the $bla_{OXA-23-like}$, which confers resistance to carbapenems.[24] These resistance islands have been described in *A. baumannii* epidemic strains belonging to the important global clones, European Clone I (EC I) and European Clone II (EC II), known for their increased capacity to spread worldwide.[22]

Several other genomic resistance islands have been fully characterized in *A. baumannii*. The majority were found in strains of EC I, such as, AbaR1, AbaR3, AbaR5, AbaR6, AbaR7, AbaR8, AbaR9, and AbaR10. These AbaRs share a structure represented by a 16.3 kb backbone transposon (Tn*6019*) interrupted by a large compound transposon that contains a variable-resistance region bounded by directly oriented copies of Tn*6018*. Exceptions are AbaR6 and AbaR7, each with a large deleted region.[25] Much less is known about AbaRs in EC II. The resistance islands harbored by this clone are integrated at the same site of the ATPase gene as is known for AbaRs in EC I.[25]

AbaR1 is the largest resistance island described to date. This island contains 86 kb and was originally described in the epidemic *A. baumannii* strain AYE belonging to ECI. This strain was responsible for outbreaks in France during 2004.[21] *A. baumannii* AYE strain revealed the presence of a large gene cluster, containing many resistance determinants, inserted into the chromosome.[21]

Of the 45 resistance genes described in AbaR1 resistance island, 25 were associated with resistance to several classes of antibiotics. These include genes that had not been previously described in *Acinetobacter* species such as *strA*, *strB*, *aphA1*, and *aac69* (encoding resistance to aminoglycosides); putative tetracycline-resistance genes *tetA* (tetracycline efflux pump) and *tetR* (repressor protein); *dfrX* (resistance to cotrimoxazole); and the chloramphenicol-resistance gene *cmlA* (chloramphenicol efflux pump). Moreover, Fournier et al. (2006) described the presence of genes in AbaR1 that encode VEB-1 and OXA-10 β-lactamases, the aminoglycoside acetyltransferase gene *aac3*, and the aminoglycoside adenyltransferases *aadA1*/DA1/B; the cotrimoxazole resistance-associated *dfrI*; *cmlA5* and one copy of the chloramphenicol acetyl-transferase *cat*; the rifampin ADP-ribosyltransferase gene *arr-2*; and five

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