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Antimicrobial resistance islands: resistance gene clusters in *Salmonella* chromosome and plasmids

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Abstract

Genes conferring simultaneous resistance to different classes of antimicrobials, confer a selective advantage to the host, particularly when those corresponding antibiotics are administered. Multiple resistance genes clustered within the same genetic locus (*resistance island*) can be transferred en bloc to other organisms. In this chapter we review novel multidrug resistance islands recently described in *Salmonella*.

Keywords: Antimicrobial resistance; Horizontal genetic transfer; Insertion sequence; Integron; Mobile genetic element; Plasmid; Resistance gene; *Salmonella*; Transposon

1. Introduction

Antimicrobial resistance arises from a complex multifactorial process confounded by a panoply of mobile genetic elements that contain and transfer resistance determinants. Use of antimicrobials in clinical and veterinary medicine is a recognized driving force for the selection of resistant bacteria. Selective pressure has resulted in the development of strains that are resistant to more than one antimicrobial agent. Acquisition of resistance genes is the predominating factor associated with emergence, evolution and dissemination of these genetic markers. Two processes are important *horizontal transfer*, where genes move from one bacterium to another, conferring their unique phenotypic characteristic(s) and *translocation*, where genes move from one location [e.g.: plasmids] to another [e.g.: chromosome]. More recently the assembly of repertoires of resistance genes as distinct clusters or antimicrobial resistance islands is now regarded as an efficient means by which the dissemination of these markers can occur *en bloc*. Mobile genetic elements together with various genetic recombination mechanisms facilitate this process. It is therefore important to understand how expanded antimicrobial use can lead to the development of multidrug resistance gene clusters.

Integrons are the latest genetic element to be recognized, and they can carry complex arrays of gene cassettes. Transposons and insertion sequences (Fig. 1) have also been frequently associated with resistance genes forming clusters of physically and functionally associated resistance determinants. These complex configurations are generally referred to as *antimicrobial resistance islands* and those found in *Salmonella* are illustrated in this review as examples of the complexity and versatility of the genetics of antimicrobial resistance. In this review the description of the antimicrobial resistance islands is preceded by a short summary of some relevant examples showing the occurrence of resistance genes in *Salmonella* associated with transposons and insertion sequences. These genetic elements are considered to be the assembly units involved in the formation of resistance islands. Their presence in the genomes of various *Salmonella* serotypes may be indicative of their importance in the development and diffusion of defined and evolving antimicrobial resistance islands.

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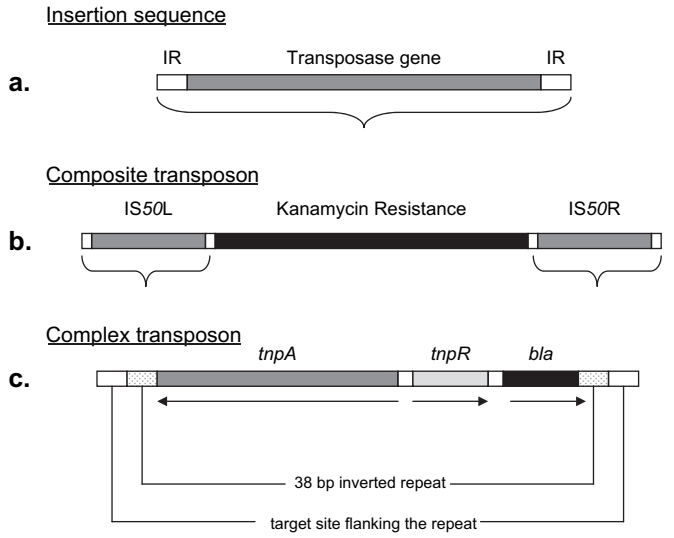

Fig. 1. Schematic illustration depicting the structure of (a) a typical insertion sequence (IS) element, (b) a composite transposon – Tn*5* and (c) a complex transposon – Tn*3*. The functional elements are illustrated in each case. [*tnpA*, transposase; *tnpR*, resolvase and *bla*, β-lactamase encoded gene].

2. Mobilization of resistance genes by transposons and insertion sequences in *Salmonella*

Transposons are mobile genetic elements (Fig. 1) that encode the necessary machinery to promote self-translocation (i.e. the transposase and the target DNA sites at which the recombinase acts) [1]. The presence of antibiotic resistance genes on transposable elements is a matter of concern with regard to the dissemination of the antimicrobial resistance. A variety of transposable elements have been recently identified that contribute to the dissemination of relevant antimicrobial resistance genes in *Salmonella*.

2.1. Transposons carrying tetracycline and aminoglycoside resistance genes

The genes coding for resistance to tetracyclines are often associated with transposons (Fig. 1b and c). The tetracycline resistance gene of hybridization class A [*tet(A)*], which encodes a membrane-associated efflux protein, is associated with the 11.1-kb non-conjugative transposon Tn*1721* [2]. This transposon has been detected on conjugative or mobilizable plasmids in various *Salmonella* obtained from different sources. Most of the *tet*(A) genes have been described within a truncated version of the transposon Tn*1721* [3,4]. This variant, was described initially in two isolates of *Salmonella* Choleraesuis and *Salmonella enterica* Typhimurium var. Copenhagen isolated from animals in Germany, and has been frequently reported in many serotypes isolated in different geographical areas [3–5].

Recent studies also identified the association of Tn*1721* with Tn*3* (Fig. 1c), a $bla_{\text{TEM-1}}$ gene-carrying transposon that mapped to conjugative and non-conjugative plasmids and the host chromosome [5]. Transposons Tn*3* and Tn*1721* exhibit similar mechanisms of replicative transposition, both have terminal inverted repeats of 35–38 bp and produce characteristic 5 bp direct repeats at their integration sites. Both Tn*1721*-associated *tet(A)* genes and the Tn*3*-associated $bla_{\text{TEM-1}}$ genes have been detected in some *Salmonella* serotypes and a Tn*3*–ΔTn*1721* fused element has also been observed on the pFPTB1 plasmid of *S*. Typhimurium [5]. This finding is interesting as it suggests that the fused Tn*3*–ΔTn*1721* element can be disseminated as a complete unit, promoting the simultaneous spread of resistance to two classes of antimicrobial agents, penicillins and tetracyclines.

The phospho-transferase *aph(6)-Ia* (*strA*) and the *aph(6)-Id* (*strB*) genes conferring streptomycin resistance, appear to be widely distributed among Gram-negative bacteria. These *strA–strB* genes have been identified in bacteria circulating in humans, animals and plants and were also described as part of Tn*5393* often located on plasmids [6]. Recently, the emergence of the *strA–strB* resistance genes has been observed in many unrelated multidrug-resistant *S. enterica* strains of different serotypes [7]. The *strA–strB* genes, in *Salmonella* of animal origin, have also been described as linked to a particular Tn*5393*-derivative, characterized by the presence of the insertion sequence IS*1133*, previously identified only in the plant pathogen *Erwinia amylovora* [3]. The insertion of these IS elements within the transposon results in an increased expression of the *strA–strB* genes [8]. The identification of the Tn*5393*::IS*1133* element in *Salmonella* suggests novel scenarios of resistance transmission among zoonotic and plant pathogens; it may be hypothesized that *Salmonella* imported this genetic element from plant pathogens probably through the contamination of animal feeds. As tetracycline and streptomycin are common antimicrobials administered in veterinary medicine their frequent use may have contributed to the successful spread of these genetic determinants in zoonotic pathogens.

The *armA* gene (*a*minoglycoside *r*esistance *m*ethylase), which confers resistance to 4,6-disubstituted deoxystreptamines and fortimicin, has been very recently described as part of a composite transposon Tn*1548*. This gene was initially found on the IncL/M plasmid IP1204 in *Klebsiella pneumoniae* that also encoded a CTX-M-3 β-lactamase. In addition it is now being reported in clinical isolates of *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *K. pneumoniae*, *Shigella flexneri*, and *Salmonella*, in which it is always associated with $bla_{\text{CTX-M-3}}$ on IncL/M plasmid as part of Tn*1548* together with the *aadA1*, *sul1*, and *dfr12* genes, conferring resistance to streptomycin/spectinomycin, sulfonamides, and trimethoprim, respectively. The genetic element is flanked by two copies of IS*6* and migrates by replicative transposition [9,10].

Aminoglycoside modifying enzymes are often encoded by gene cassettes located within class 1 and class 2 integrons. Class 1 integrons are commonly associated with various transposons including Tn*21* (Fig. 3a), Tn*1696*, and Tn*1412* of the Tn*3* family [11]. The Tn*21* transposon, in particular, carries the In*2* integron (Fig. 3a), encoding streptomycin/spectinomycin resistance encoded by the *aadA1* gene, which is found widely distributed in Gram-negative and -positive bacteria.