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Review

Transfer of antibiotic-resistance genes via phage-related mobile elements

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ABSTRACT

Antibiotic resistance is a major concern for society because it threatens the effective prevention of infectious diseases. While some bacterial strains display intrinsic resistance, others achieve antibiotic resistance by mutation, by the recombination of foreign DNA into the chromosome or by horizontal gene acquisition. In many cases, these three mechanisms operate together. Several mobile genetic elements (MGEs) have been reported to mobilize different types of resistance genes and despite sharing common features, they are often considered and studied separately. Bacteriophages and phage-related particles have recently been highlighted as MGEs that transfer antibiotic resistance. This review focuses on phages, phage-related elements and on composite MGEs (phages-MGEs) involved in antibiotic resistance mobility. We review common features of these elements, rather than differences, and provide a broad overview of the antibiotic resistance transfer mechanisms observed in nature, which is a necessary first step to controlling them.

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1. Introduction

Bacterial genomes exhibit dynamic plasticity and are shaped by horizontal gene transfer (HGT), genome rearrangement, and the activities of mobile DNA elements (Darmon and Leach, 2014). The number of reports of HGT mechanisms between distinct organisms has

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increased substantially in the recent years, not only for bacteria, but also for eukaryotic cells (Keeling and Palmer, 2008). HGT vectors suffer a dual evolutionary pressure on their survival: via vertical gene transfer (VGT) from parenteral strains to their progeny and by HGT via, at least, the three well known mechanisms: conjugation, transformation and transduction. Some of these mechanisms are mediated by mobile genetic elements (MGEs) (Gogarten and Townsend, 2005).

Many MGEs are able to capture bacterial DNA and move it between hosts. The collection of genes present in one species can then potentially be transferred to many others (Bushman, 2002). Horizontal mobilization broadens the gene repertoire available to organisms, improving their chances to evolve. Bacterial genes may be randomly recruited from the original host into the recipient cell, but they are selectively kept only if they confer advantage on the new host strain through a marked impact on its fitness. Mechanisms of HGT are responsible of phenotypic variability in metabolism, virulence and antibiotic resistance.

Bacteria have developed mechanisms of resistance that combat the threat of different antibiotics produced by competitor microorganisms. While some bacterial strains display intrinsic resistance (Davies and Davies, 2010), in others antibiotic resistance is acquired by mutations in different chromosomal loci, by the recombination of foreign DNA into the chromosome or by horizontal acquisition of antibiotic resistance genes (ARGs) (Davies, 1997). In many cases, these three mechanisms operate together. For example, the resistance to a given antibiotic acquired by mutation of the antibiotic target gene could later be transferred laterally by an R-plasmid or a temperate phage. DNA fragments encoded in an MGE can recombine either with the bacterial chromosome or with other elements present in bacterial cells. In addition, many MGEs have the capacity to insert themselves into the bacterial chromosome, resulting in chromosomally-encoded resistance. This insertion could be either reversible or irreversible, depending on the element. If irreversible, the element loses its intrinsic horizontal mobility, while other MGEs always remain as independent replicons and can be horizontally transferred. Because of the clear advantages provided by the incorporation of ARGs, there is a variety of HGT mechanisms that have generated a considerable range of elements. Such diversity leads to the need for continuous adaptation and classification and to the generation of new terms and definitions of the intermediate elements.

In this review, we focus on composites within gene transfer pathways that result in intermediate or composite elements that mobilize ARGs, and particularly, on those intermediates that involve phages or phage-derived particles that transfer ARGs.

2. Classic elements involved in ARG transfer

A common trend in science is to organize reality into clusters, sections, types and so forth, with the intention of providing some order and structure that could help us to understand the diversity we find in the world. However, sometimes the specificity of the classifications prevents wider observations of the big picture.

Many of the elements that we present in this section share common features. There is a group that replicates independently of the host chromosome while there are some that could become integrated into bacteria. Among the latter, the most common trait is the presence of integrases: the enzymes that allow insertion of the element into the host chromosome. Many integrases are members of the tyrosine recombinase family (Esposito and Scocca, 1997). Many MGEs, such as phages, plasmids, genomic islands or integrative conjugative elements (ICEs) (Boyd et al., 2009; Casjens, 2003; Muniesa et al., 2006; Wozniak and Waldor, 2010), provide the required integrase genes, while some MGEs hijack integrase genes located in the host bacterial chromosomes (Das et al., 2013). Many of these elements can revert from their integrated state and excise themselves from the chromosome similarly to how temperate phages do. In the extracellular state, they are susceptible to movement between cells. The horizontal mobility mechanisms will depend on the proximity of the donor cell to the recipient.

2.1. MGEs that mediate ARG transfer with cell–cell contact

The most evident difference between the elements that mobilize ARGs is the requirement for cell-to-cell contact, or lack thereof. The mechanism that requires contact is conjugation, which operates in the transfer of plasmids, transposons, integrons, and other related elements (Fig. 1).

Plasmids are elements that have been widely explored as the purveyors of antibiotic resistance mobility and have been found to allow for the rapid development of multiple antibiotic resistance. Plasmids are capable of replicating together with the cell as self-replicating elements and to transfer resistance vertically, or to be mobilized horizontally by incorporation into a conjugative plasmid. ARGs can be conjugally transferred to cells from a broad range of organisms; in Gram-negative bacteria the process is mediated by the type IV secretion system (T4SS) (Cabezón et al., 2014). Some plasmids can also be inserted into the bacterial chromosome (Boccard et al., 1989) and mobilized vertically.

Chromosomal resistance can also often be captured in a transposon (Chancey et al., 2012; Quintiliani and Courvalin, 1996). The way in which transposons are integrated into and excised from the chromosome depends on whether they are “autonomous” or “non-autonomous”. Autonomous transposons move by themselves; while non-autonomous transposons require the presence of other transposons to move. Integration is dependent on the presence of a transposase that recognizes direct repeats, but the main point is that transposons *per se* are not transferred horizontally. Transposons could be simple or composed. Simple transposons are in fact insertion sequences (IS), that do not possess ARGs, but can contribute to variations in antibiotic resistance by moderating the expression of contiguous genes (i.e. introducing strong promoters), mobilizing contiguous genes or simply inactivating genes. IS are flanked between short, inverted, repeated sequences that flank its gene coding region. Composite transposons, in comparison to simple transposons have genes, often ARGs, flanked by two separate and not always identical IS elements. The entire fragment of DNA spanning from one IS element to the other is transposed as one complete unit.