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Beyond the canonical strategies of horizontal gene transfer in prokaryotes

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Efforts to identify and characterize strategies for horizontal gene transfer (HGT) in prokaryotes could have overlooked some mechanisms that do not entirely fit in with the canonical ones most often described (conjugation of plasmids, phage transduction and transformation). The difficulty in distinguishing the different HGT strategies could have contributed to underestimate their real extent. Here we review non classical HGT strategies: some that require mobile genetic elements (MGEs) and others independent of MGE. Among those strategies that require MGEs, there is a range of newly reported, hybrid and intermediate MGEs mobilizing only their own DNA, others that mobilize preferentially bacterial DNA, or both. Considering HGT strategies independent of MGE, a few are even not restricted to DNA transfer, but can also mobilize other molecules. This review considers those HGT strategies that are less commonly dealt with in the literature. The real impact of these elements could, in some conditions, be more relevant than previously thought.

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Horizontal gene transfer (HGT) constitutes the major evolutionary mechanism for prokaryotes, and it is of great concern for modern medicine [1,2]. Bacteria adapt to their environment by incorporating genes that provide selective advantages and which are transferred between cells of the same generation, providing a unique mechanism of genetic exchange [3,4]. Prokaryotes have developed different strategies for HGT, by using mechanisms that can be dependent or independent of mobile genetic elements (MGEs). The canonical well-known mechanisms are transformation, conjugation and transduction and the canonical MGEs are plasmids, transposons and bacteriophages. However, the last years, the list of HGT strategies has been expanded beyond the canonical ones.

Attempts to classify the different HGT strategies are sometimes limited and tend to simplify the inherent complexity found in nature. There are some elements that could not be considered as 'canonical', but that contribute actively to HGT in prokaryotes; and some of these contributions may be more relevant than previously believed. This underestimation could have been caused by difficulties in specifically detecting these elements without confusing them with other MGEs, in distinguishing them from the core bacterial genome [5], or because newly described MGE are using 'canonical' mechanisms of transfer and can therefore be mistaken for the classical elements.

This review considers HGT strategies beyond the classical ones, and classify them in two groups (Figure 1): (A) strategies involving MGEs and among these we distinguish between elements that mobilize only their own DNA or those that mobilize, exclusively or in addition, bacterial DNA and, (2) strategies that do not require MGE to mobilize DNA.

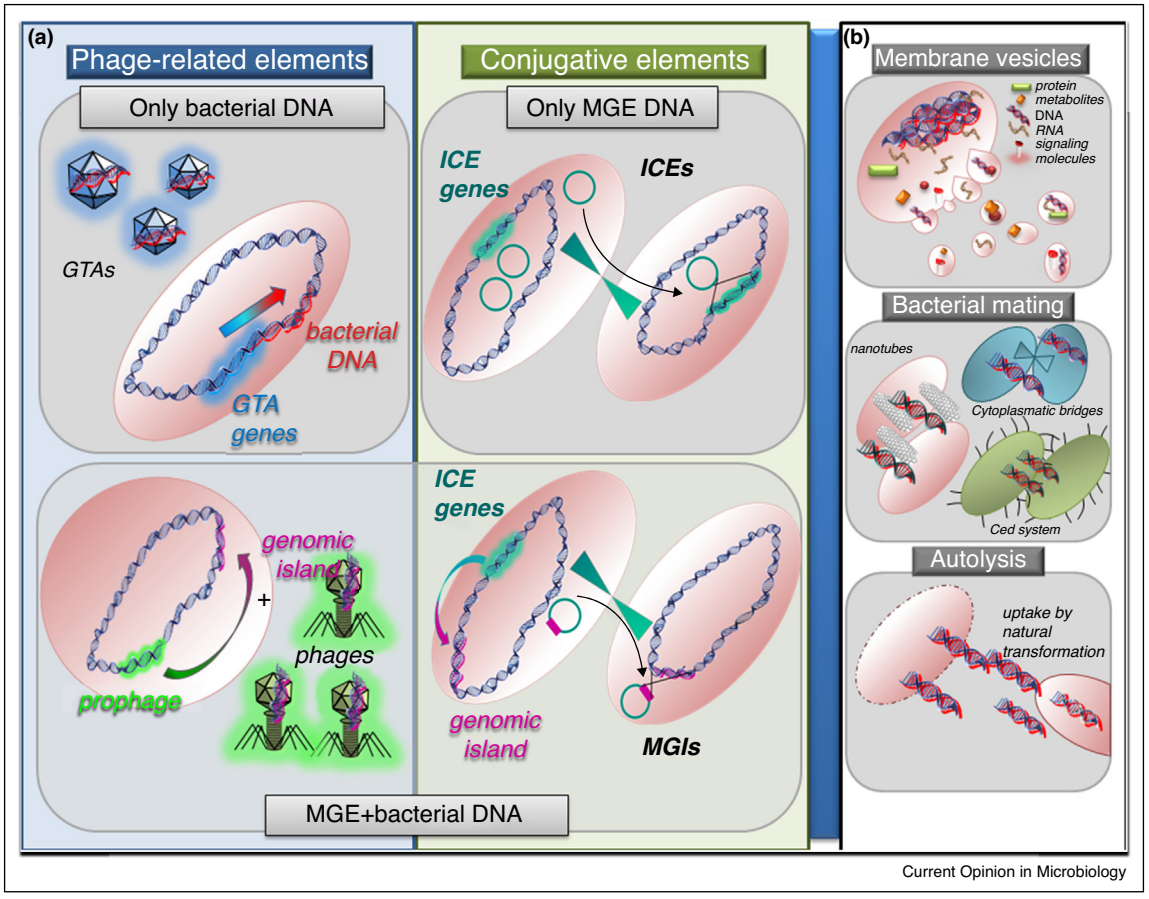
HGT strategies involving MGEs

The evolutionary goal of a MGE should be to perpetuate itself by spreading its own genetic material. In addition to it, and almost accidentally, transfer of bacterial DNA may take place. However, evidences show that in certain bacterial groups some MGEs have evolved, losing their ability to mobilize its own DNA and mobilizing preferentially the bacterial DNA, providing a clear benefit for the host. Here, we review some of these strategies.

HGT strategies involving MGEs that only mobilize bacterial DNA

In the seventies, a new phage-related element capable of transferring DNA between strains [6] was discovered in the marine bacterium *Rhodobacter capsulatus* (formerly known as *Rhodopseudomonas capsulata*): the *gene transfer agent* (GTA) [7] (Figure 2). GTA genes encode bacteriophage-capsid structures (sometimes tailed), but unlike phages, they do not require previous infection by a phage, since the genes for the capsid are already present within the cell chromosome. The capacity to form GTAs allows *Rhodobacter* to package, spread and transfer a random piece of its genome (<15 kb in size, Table 1) through cell lysis and transduction (if it could be

Figure 1



Schematic diagram of the mechanisms involved in HGT in prokaryotes according with the strategy used. **(a)** HGT strategies requiring MGE and the ability to mobilize their own DNA, their own DNA + host DNA, or only host DNA. **(b)** HGT strategies independent of MGE. In blue, bacterial DNA. Blue DNA with green shadow for prophage genes, blue shadow for GTA genes, turquoise shadow and turquoise circles for ICE DNA, red shadow mobilized bacterial DNA, purple shadow DNA and purple square mobilized genomic island.

considered as such) to other recipient bacteria. This strategy is considered a relevant driver of genetic transfer in this genus [8••]. *R. capsulatus* GTA gene homologues are widespread in many marine α-proteobacteria [9] and could share a common ancestor [10]. Other genetically unrelated GTAs have also been identified in other bacteria (Table 1). The origin of GTAs is believed to be related with phages, which is supported by the resemblance of their DNA sequences and their capsid proteins [11,12]. It is believed that GTA could have evolved from prophages in the genome of these bacteria, that have segregated the major part of the prophage DNA and kept the prophage structural genes encoding the capsid and the packaging machinery [8••,13]. These could serve for bacterial genetic exchange without the threat of virus propagation, as there are no phage genes that can orchestrate phage propagation but also because GTAs do not package their own genes as discussed below.

Production and release of GTA is not entirely understood. It is restricted to a part of the bacterial population [14] and dependent on a number of factors, including growth phase, phosphate concentration, and a putative phosphorelay system involving homologues of cell cycle regulatory proteins CtrA, ChpT and CckA [9,14,15].

GTAs display differences from generalized transduction phage particles, one of the most remarkable is that GTA-mediated transduction shows a higher efficiency than generalized transduction [8••]. Also DNA transfer by GTAs differs from specialized transduction, because specialized transduction mobilizes a small fragment of bacterial DNA located next to the prophage insertion site. Moreover, GTAs differ from temperate prophages, which insert the whole phage genome into the bacterial chromosome [8••], while GTA is still present in the bacterial genome but does not mobilize their own genes when activated. The almost inexistent mobilization of GTA