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Trends in Microbiology

Spotlight

Agents of change: a partnership between mobile genetic elements facilitates rapid bacterial adaptation

Elizabeth S. Duan[1], Olivia Kosterlitz[2], and Benjamin Kerr[1,*]

While the evolutionary interests of mobile genetic elements may differ from those of their bacterial hosts, these elements can be beneficial for their hosts by delivering, disrupting, or activating genes. A recent paper by Sastre-Domínguez *et al*. describes a novel synergistic effect of mobile elements in clinically relevant bacteria, whereby conjugative plasmids that carry transposable elements can be agents of rapid adaptive change through an elevation in transposition-mediated mutation rate.

Mobile genetic elements (MGEs) present a double-edged sword to their bacterial hosts as they can produce both costs and benefits. Costs can result from MGE modes of replication that are independent from that of their hosts [1,2]. For instance, plasmids that replicate as they move between hosts can impose fitness costs, and transposable elements that replicate as they jump within a host genome can disrupt essential genes [1,3]. However, MGEs can also provide benefits to their hosts. Transposition can have beneficial effects when genetic disruption or genomic rearrangement enables rapid adaptation to stressful conditions [3]. Conjugative plasmids can shuttle adaptive genes between hosts, mediating bacterial adaptation in clinically and environmentally important contexts by delivering such genes (e.g., antibiotic resistance, virulence factors, or heavy-metal tolerance) [4]. A recent study by Sastre-Domínguez *et al*. shows that plasmids can carry not only genes that immediately benefit their bacterial host (Figure 1A,B), but also insertion sequences (ISs) that can provide a unique benefit: the potential of future adaptive change through an increase in the IS-mediated mutation rate (Figure 1C) [5].

Combining experimental evolution and clinical sequence analysis, Sastre-Domínguez *et al*. found that transposition of insertion sequence 1 (IS1) from the conjugative plasmid pOXA-48 to its host genome promoted adaptation. In the laboratory, they evolved clinical isolates of *Escherichia coli, Klebsiella pneumoniae,* and *Citrobacter freundii* carrying pOXA-48, harboring IS1, for 100 generations. They identified mutations attributed to IS1 movement that disrupted stress response, fimbrial, and capsule operons, which are predicted to increase host fitness in laboratory conditions. Interestingly, their clinical analysis produced a similar story. Genomic sequencing of a series of pOXA-48-carrying isolates from the same set of patients revealed genomic mutations mediated by IS1 transposition. These genetic changes [e.g., to lipopolysaccharide (LPS), O-antigen composition, and resistance factors] are predicted to be pathoadaptive, suggesting that plasmid-mediated IS1 transposition is a clinically relevant mode of rapid adaptation.

The authors then investigated the regulation mechanism behind IS1 transposition and found that the transposition-mediated mutation rate depended on IS1 copy number. Using a *K. pneumoniae* strain carrying few genomic IS1 copies, they performed a fluctuation test, elegantly demonstrating that the addition of pOXA-48 (which harbors two IS1 copies) increases the transposition-mediated mutation rate. However, if they further increased IS1 copies (by inducing IS1 on an additional engineered multicopy plasmid), the mutation rate decreased. In this way, the rate of IS1 transposition appears to exhibit a non-monotonic relationship with copy number, increasing when copies are few and decreasing as copies become more common. Thus, while an incoming plasmid harboring IS1 may be relatively inert in a host with a high genomic IS1 copy number, it may mediate a burst of mutation in a host with a low genomic copy number, boosting the supply of beneficial change underpinning rapid adaptation.

As noted by the authors, this plasmid–IS partnership carries potential benefits not only for the host bacterium but also for the plasmid and the IS partners themselves. For the plasmid, coevolution with its bacterial host can ameliorate plasmid carriage costs. Thus, carrying an IS that promotes rapid adaptation could hasten coevolution and contribute to plasmid persistence (i.e., a potential resolution of the 'plasmid paradox' [1]). For the IS, given negative regulation by its own copy number, hitching a ride on a conjugative plasmid provides access to new hosts with low genomic copies, thereby facilitating its spread. For the bacterial host, this plasmid–IS partnership acts as a vehicle that induces a regulated burst of adaptation by generating future beneficial mutations (Figure 1C,D) [6].

To further understand the general impact of this mechanism in microbial communities, each player – plasmid, transposable element, and host – should be considered. For IS1, the transposition-mediated mutation rate is negatively regulated by copy number [5]. As the genomic IS1 copy number differs between species (also found by the authors within the three species they explored), changing the bacterial host may impact how incoming plasmid–IS partners

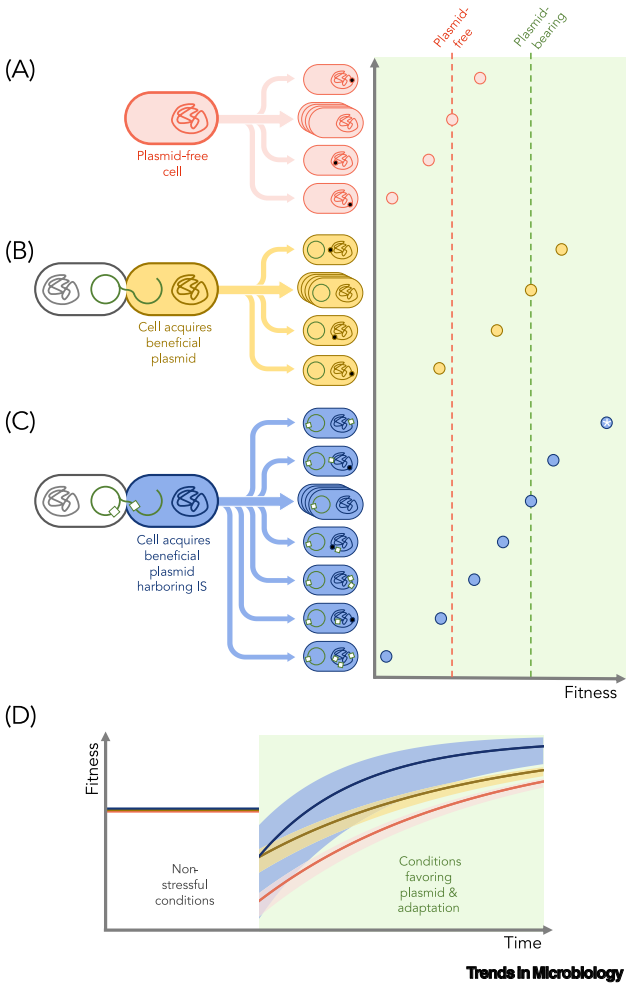

Figure 1. A schematic of bacterial adaptation in the presence and absence of mobile genetic elements (MGEs). (A) A plasmid-free bacterial cell (red), (B) a plasmid-containing cell (yellow), and (C) an insertion sequence (IS)-harboring-plasmid-containing cell (blue) generate beneficial mutants (upward-curving arrows) and deleterious mutants (downward-curving arrows) during a period of growth (straight arrows). The plotted dots give the fitness of each cell in an environment favoring the plasmid. The addition of a plasmid harboring IS copies (small white squares) increases the transposition-mediated mutation rate of (C) over that of (A) and (B), which rely only on non-IS-related mutations (small black circles) to generate variation. This results in an increased likelihood of generating a highly beneficial mutant (asterisk). (D) Although all bacteria eventually adapt to the new environment (green background), the IS-harboring-plasmid-containing cells (blue, C) adapt faster due to the plasmid–IS partnership increasing mutational supply. For the new environment, the ranges of mutant fitness for the three types of cells are shown as bands around the average fitnesses (lines with colors matching A–C).

affect mutation rate. Different plasmids with different plasmid copy numbers will also change IS1 copy number, enhancing or dampening its effect on the mutation rate. Finally, different plasmids carry different transposable elements that have replication and regulation mechanisms that differ from that of IS1 [2,3]. Thus, different MGE partnerships may magnify or reduce the kind of transposition-mediated mutational effects described for IS1 and pOXA-48, modifying the potential for adaptive change.

Besides the players, the environmental context could additionally make the benefits of this plasmid–IS partnership conditional. In unchanging environments in which strains are already well adapted, transposition-mediated genetic rearrangement may be largely costly. Using the same experimental evolutionary approach as the authors, this idea could be tested using strains pre-adapted to laboratory conditions. On the flip side, stressful conditions may set the ideal stage for IS-mediated change delivered by a plasmid [3]. This may be the case in clinical contexts, where IS-harboring plasmids mobilize mutational potential together with adaptive accessory genes, facilitating rapid pathoadaptation.

Of particular relevance to clinical contexts, there are additional implications for partnerships between transposable elements and plasmids when considering the spread of drug resistance. It is important to note that more complex transposons can carry antibiotic-resistance genes. Thus, replicative transposition could not only promote adaptation via genomic rearrangement but could also increase antibiotic resistance by raising the dosage of its cargo [7,8]. Intracellular transposition between plasmids could also result in the creation of novel multidrug-resistant plasmids. Altogether, plasmids harboring transposable elements present important avenues for the evolution of antibiotic resistance, offering multiple routes to improved resistance and the generation of new forms of mobile multidrug-resistance elements [9].

This study demonstrates the importance of MGEs as a tool for bacteria to rapidly alter their genetic architecture, allowing them to adapt to changing environments. As many distinct MGEs are ubiquitous in microbial communities, the results of Sastre-Domínguez *et al*. highlight that interactions between MGEs merit more attention, where novel synergistic effects may yet be uncovered. Future research should be directed towards a better understanding of how partnerships, among genetic elements that move between and within their hosts, can impact the evolution of their hosts.

Acknowledgments

We thank Shivani Hargunani, Jana S. Huisman, Chenxi Liu, Imraa Omar, Álvaro San Millán, Alfonso Santos-López, Jorge Sastre-Domínguez, Maddy Scott, and Beth Traxler for useful suggestions on the article. This material is based upon work supported by the Environmental Biology Division from the National Science Foundation (grant number 2142718 to B.K.). and the NSF Postdoctoral Research Fellowships in Biology Program (grant number DBI-2305907 supporting O.K.).

Declaration of interests

The authors declare no competing interests.

[1]Department of Biology, University of Washington, Seattle, WA, USA
[2]Department of Biological Sciences, University of Idaho, Moscow, ID, USA

*Correspondence:
kerrb@uw.edu (B. Kerr).

https://doi.org/10.1016/j.tim.2024.10.010

References

1. Brockhurst, M.A. and Harrison, E. (2022) Ecological and evolutionary solutions to the plasmid paradox. *Trends Microbiol.* 30, 534–543
2. Ares-Arroyo, M. *et al.* (2024) Hijackers, hitchhikers, or co-drivers? The mysteries of mobilizable genetic elements. *PLoS Biol.* 22, e3002796
3. Kidwell, M.G. and Lisch, D.R. (2001) Perspective: transposable elements, parasitic DNA, and genome evolution. *Evolution* 55, 1–24
4. Partridge, S.R. *et al.* (2018) Mobile genetic elements associated with antimicrobial resistance. *Clin. Microbiol. Rev.* 31, e00088
5. Sastre-Domínguez, J. *et al.* (2024) Plasmid-encoded insertion sequences promote rapid adaptation in clinical enterobacteria. *Nat. Ecol. Evol.* 8, 2097–2112
6. Wu, Y. *et al.* (2015) Dynamics of bacterial insertion sequences: can transposition bursts help the elements persist? *BMC Evol. Biol.* 15, 288
7. Nicoloff, N. *et al.* (2024) Three concurrent mechanisms generate gene copy number variation and transient antibiotic heteroresistance. *Nat. Commun.* 15, 3981
8. Maddamsetti, R. *et al.* (2024) Duplicated antibiotic resistance genes reveal ongoing selection and horizontal gene transfer in bacteria. *Nat. Commun.* 15, 1449
9. Kadibalban, A.S. *et al.* (2024) The extent and characteristics of DNA transfer between plasmids and chromosomes. *Curr. Biol.* 34, 3189–3200