From passengers to drivers
Impact of bacterial transposable elements on evolvability

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Microbes have several mechanisms that promote evolutionary adaptation in stressful environments. The corresponding molecular pathways promote diversity through modulating rates of recombination, mutation or influence the activity of transposable genetic elements. Recent experimental studies suggest an evolutionary conflict between these mechanisms. Specifically, presence of mismatch repair mutator alleles in a bacterial population dramatically reduced fixation of bacterial insertion sequence elements. When rare, these elements had only a limited impact on adaptive evolution compared with other mutation-generating pathways. IS elements may initially spread like molecular parasites, but once present in many copies in a given genome, they might become generators of novelty during bacterial evolution.

Insertion sequence (IS) elements are small transposable genetic elements widely distributed in bacterial genomes.1 They are generally very short and contain only the genetic information essential for their transposition.2 By inserting to new genomic locations, they frequently inactivate or upregulate flanking genes. By inducing recombination events, they also cause deletions and inversions of large genomic segments.3 Several lines of observations point to the direction that the net effects of transposon insertions are harmful for the host.3 First, direct experimental evidences indicate that enhanced mobilization of transposable elements are generally deleterious.4,6 Second, most IS families are found only in a limited number of species.5,7 However, within any one genome, they are typically present in many copies which are very similar to each other.7 This is reminiscent to the evolutionary dynamics of other genomic parasites,8 such as retroviruses. Both retroviruses and IS elements have entered bacterial genomes only very recently and spread through horizontal gene transfer across species. Third, to minimize damage they may cause during insertions, these elements have become suppressed by host regulatory factors,9 or reside in genomic regions where they cause less harm.6

If harmful, why are they present, even if transiently, in bacterial genomes? One answer may be that in sexual populations, IS elements spread as selfish entities10 even if they deliver no beneficial effects.11 Indeed, these elements are nearly always autonomous, i.e., the genes necessary for transpositions are encoded by the elements and not by the host genome. One prediction of the theory is that bacterial species with numerous IS elements should also have more genetic exchange.12

A preliminary analysis failed to find strong support for this idea. Recently, Multi Locus Sequence Typing (MLST) data sets of bacterial and archaeal species were analyzed to explore the ecological and phylogenetic determinants of recombination frequency differences across species.13 The authors compiled a data set on the estimated ratio of nucleotide changes as the result of recombination relative to point mutations13 for 48 species. In agreement with previous studies, the data suggest that homologous recombination rates vary widely between species. Another work6 reconstructed the distribution of

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First, we need to understand the evolutionary forces driving gradual accumulation of these elements in nascent bacterial genomes. Second, given the wealth of other molecular pathways that boost bacterial mutation rate under times of stress, the interplay between them must be considered. To what extent does the presence of one such mechanism in the population influence the evolutionary fate of IS elements? Here we briefly summarize our current, but still rather limited state of knowledge on these issues.

When a given family of IS elements invades an initially transposon-free bacterial genome, the process is expected to start with a single or very few copies. Do they produce a sufficient number of mutations to be favored by selection? Answering this question is not straightforward, as it requires comparison of evolvability of genotypes with differences in the number of residing IS elements only.

Our lab took advantage of the availability of a *Escherichia coli* MDS42, a strain with a reduced genome devoid of all mobile genetic elements and cryptic virulence factors. This strain has several
mutagenesis hinders evolution of constitutive mutators, and sex promotes mutational robustness. Future studies should investigate the interplay between these systems.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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This is a potentially problematic result for the mutator theory of transposable elements. IS elements may have to reach a critical number in the host genome to have a substantial impact on genome evolution. Prior to that point, bacteria could adapt more efficiently by other means, including defective MMR alleles. At the moment, we can only speculate how transposition rate depends on IS copy number and how the transition from a selfish element to a mutator beneficial for the host can take place in natural populations (Fig. 2).

Another, largely neglected issue is the long-term consequences of IS elements and other mutator alleles on survival. Once a mutator allele has spread in a bacterial population and stressful conditions are over, they will generate largely harmful mutations. Due to this long-term disadvantage, MMR deficient mutator alleles arise frequently, but low mutation rate can be restored through gain of functional variants through horizontal transfer. IS elements may have a serious advantage over constitutive mutator alleles. They are activated only under stressful conditions, and hence they may not enhance mutation load substantially.

These issues represent only the tip of the iceberg. Evolutionists suggested several key candidate molecular systems driving bacterial evolution. Pioneering works claim that mutators and sex are conflicting adaptive strategies, stress-induced mutagenesis hinders evolution of constitutive mutators, and sex promotes mutational robustness. Future studies should investigate the interplay between these systems.

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