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The SOS Response Controls Integron Recombination

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Integrons are bacterial genetic elements capable of incorporating and expressing promoterless genes as cassettes (1). Two subsets of integrons have been described: mobile (or resistance) integrons (MIs), which are located in transposons and contain two to eight cassettes encoding resistance to a broad spectrum of antibiotics, and chromosomal integrons (CIs), which are ancient sedentary elements that may contain hundreds of gene cassettes of mostly unknown function. Several lines of evidence indicate that MIs and their cassettes were derived from CIs (1). All integrons contain an integrase gene (inti) that mediates the integration of exogenous gene cassettes at the attI site and random excision or rearrangement of resident gene cassettes (fig. S1). Despite the importance of integrons in the acquisition and spread of antibiotic resistance determinants, little is known about the dynamics and regulatory control of cassette recombination.

To address this issue, we aligned the upstream region of CI and MI integrase genes and identified a conserved LexA-binding motif overlapping the putative promoter regions (2) (Fig. 1A). LexA is the transcriptional repressor governing the SOS response, a widespread regulatory network aimed at addressing DNA damage by repairing or bypassing lesions (3). Derepression of SOS genes results from the autocatalytic cleavage of LexA, a process induced by single-stranded DNA and mediated by RecA. The SOS response has strong links with bacterial adaptation and has been implicated in clinically relevant phenotypes, such as dissemination of virulence factors.

We assessed the functionality of the identified Vibrio cholerae LexA-binding site in vitro and found that purified V. cholerae LexA specifically bound the identified motif, whereas changes in key site positions prevented this interaction (fig. S2). We analyzed the integrase expression in both the CI of V. cholerae and a class 1 MI of Escherichia coli. Induction of the SOS response increased the expression of a β-galactosidase reporter of integrase transcription by 4.5-fold in E. coli and 37-fold in V. cholerae. No induction was observed when either LexA or RecA was impaired or when the LexA boxes were inactivated (Fig. 1, B and C). To verify that the induction of integrase expression results in functional cassette recombination, we measured the frequency of cassette excision. For the class 1 MI and V. cholerae CI, the excision rates increased by 141-fold and 340-fold, respectively, upon SOS induction (Fig. 1, B and C). All together, these results demonstrate that the regulation of these integrase genes is strictly dependent on the SOS response and that SOS induction controls the rates of cassette recombination.

In integrons, newly acquired cassettes are highly expressed by the Pc promoter, but they can be silenced by untimely recombination events that displace the cassettes to distal positions (4). Recombination can also activate silenced cassettes or retrieve new cassettes from surrounding bacterial communities (1). Under normal conditions, SOS repression of intI maintains integron cassette arrays in a steady state. The SOS response can be induced by several stresses (5), thus ensuring that the reordering of existing cassettes and the acquisition of exogenous cassettes occur under conditions when innovations are needed. In this respect, it is worth noting that antibiotics known to induce the SOS response, such as trimethoprim, quinolones, and β-lactams, promote integrase expression (Fig. 1, B and C).

Current policies in the fight against antibiotic resistance rely on the assumption that resistance mechanisms are costly to the bacteria that host them, which thus gives these bacteria a selective disadvantage and leads to their loss in the absence of antibiotic exposure (6). However, the incorporation of responsive regulation in integrons indicates that antibiotic resistance genes can be silenced at no biological cost until needed, while other adaptive traits continue to be expressed. This being so, there may be little selection acting on MIs, and antibiotic resistance may persist in bacterial populations. Future antibiotic restriction guidelines should take this phenomenon into account.

References and Notes
2. Materials and methods are available as supporting material on Science Online.
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Supporting Online Material
www.sciencemag.org/cgi/content/full/324/5930/1034/DC1
Materials and Methods
Figs. S1 to S3
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