URLs

Escherichia coli:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=Overview&list_uids=225

gyrA:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=946614
LexA: http://us.expasy.org/uniprot/P03033

MICROBIAL GENETICS

Embrace your inhibitions

A thought-provoking new study indicates that inhibiting mutation in the genomes of pathogenic bacteria might be a viable strategy for dealing with the growing problem of antibiotic resistance.

Floyd Romesberg and colleagues used resistance to ciprofloxacin in *Escherichia coli* as their model system. Ciprofloxacin interferes with the action of topoisomerases, so mutations in topoisomerase-encoding genes (such as *gyrA*) confer ciprofloxacin resistance in bacteria. Previous work indicated that, when challenged with antibiotics, bacteria actively induce proteins that promote such mutations.

The SOS response — a DNA-repair process that is triggered by the autoproteolytic activity of the gene repressor LexA — was thought to be a key component of the mutation-induction process. The authors used a mouse-thigh infection model to show that LexA was indeed involved: a LexA-mutant form of *E. coli* (*lexA* (S119A)) did not develop resistance to ciprofloxacin, whereas 3% of the control-strain population did so within 72 hours. Repeating these experiments with an antibiotic from a different class — rifampicin — produced qualitatively similar results.

The authors followed up these studies with *in vitro* experiments that allowed them to compare the number of ciprofloxacin-resistant mutants arising before and after exposure. From these experiments, they estimated that ciprofloxacin increases the rate of evolution of resistance in control strains of *E. coli* by a factor of 10^4. By contrast, the post-exposure mutation rate was 100-fold lower in the *lexA* (S119A) strain, confirming the *in vivo* finding that LexA derepression is necessary for efficient induction of resistance.

In an attempt to identify the downstream components of the pathway that LexA triggers, Cirz *et al.* then undertook a series of similar studies of pre- and post-exposure mutation rates for different *E. coli* strains with deletions in various genes that are involved in candidate pathways. These experiments provided clear-cut evidence that both nucleotide-excision-repair and recombinational-gap-repair pathways are not involved, whereas RecBC-mediated homologous recombination is. Moreover, the authors showed that the effect of deleting any of the three LexA-repressed DNA polymerases (Pol II, Pol IV and PolV) was equivalent to preventing LexA cleavage, so it seems that LexA acts through derepression of all of these enzymes to induce mutations.

The authors suggest that the recombinational-DNA-repair pathway might also underlie bacterial responses to other antibiotics, and indeed other cellular challenges. Such a neat system of mutational feedback designed to restore the evolutionary status quo certainly has an intuitive appeal. Moreover, if true, it would also have huge implications for our understanding of, and therapeutic approach to, antibiotic resistance.

Nick Campbell, Executive Editor, Heredity

References and links

ORIGINAL RESEARCH PAPER Cirz, R. *et al.* Inhibition of mutation and combating the evolution of antibiotic resistance. *PloS Biol.* **3**, e176 (2005)