EVOLUTION

Selection always hits the bullseye

Master regulatory genes could be important targets for natural selection at times of major change. A study in a bacterial model system has dissected the molecular and fitness consequences of selection on such a regulator during colonization of a novel environment.

The authors used the simplified but ecologically plausible scenario of an *Escherichia coli* strain colonizing bacteria-free mice. They found that passage through such mice selected for a phenotypically distinct *E. coli* variant. Using a plasmid library of the ancestral genome to restore the ancestral phenotype in eight independently evolved strains, and sequencing of the candidate regions, they found that each evolved strain had been selected because of a different mutation, but all the mutations were at the same locus, *ompB*, which encodes the *EnvZ–OmpR* two-component response regulator.

The mutations did not cause loss of function; instead they shifted the balance between phosphatase and kinase activity, thereby altering the expression levels of the genes that are regulated by this master regulator. As the mutants showed reduced motility and osmotic permeability — traits that might aid survival in certain

intestinal niches — the authors looked specifically for changes in expression in *flagellin* and *porin* genes, both of which they found to be reduced.

Simply looking at the many phenotypic changes caused by these mutations in a master regulator is not sufficient to discern which of the changes are responsible for the selective advantage. So the authors ran their selection experiments with bacteria in which the expression levels of flagellin and/or porin genes had already been artificially reduced. In both cases, the *ompB* mutants that arose spontaneously during the experiment had a smaller selective advantage than when the experiment was run with the wild-type ancestor. This showed that the flagellin decrease and the porin decrease each explained some, but not all, of the selective advantage. The effects were roughly additive, with the double mutant ancestors having even less of a selective disadvantage against the *ompB* mutants.

This experiment shows that mutations in a master regulator are

consistently selected in a particular ecological situation, and that several of the pleiotropic consequences of such mutations contribute to the selective advantage. Such master switches have arisen because of the benefit to organisms that are coping physiologically with changing environments; the consequence of this might be that these master switches are also important targets of selection when the environmental changes are particularly large, with mutation representing an extra evolutionary gear for fine-tuning physiological adaptation.

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ORIGINAL RESEARCH PAPER Giraud, A. et al. Dissecting the genetic components of adaptation of *Escherichia coli* to the mouse gut. *PLoS Genet.* 4, e2 (2008)