GENE REGULATION

Plastic switches

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Uri Alon's laboratory: <http://www.weizmann.ac.il/mcb/UriAlon/index.html>

If we omit the details, then gene expression can be defined as resulting from the way in which a gene integrates the signals that operate on its regulatory control elements. But how do we describe the effects of these regulators (the 'input function'), and how do they evolve? A combined theoretical and experimental study now shows that mutations in a bacterial promoter do not simply abolish an input function but rather alter its nature, so that the promoter integrates signals in a qualitatively different way.

The *lac* operon of *Escherichia coli* is one of the most studied and best characterized of gene expression systems: this operon is controlled by *cis* elements that integrate signals from two molecules, the cAMP receptor protein and the Lac repressor. What

is curious about this regulatory system is that the logic of the input function is intermediate between an AND and an OR gate — in practice, this means that, for example, there are two threshold levels for each input rather than just one.

What would happen if mutations disrupted this elaborate system? Avraham Mayo and colleagues generated a library of 62 point mutant combinations in the upstream control region of the *lac* operon: the input function of the mutant promoters was then assessed by placing each one upstream of *GFP*, and measuring expression levels in living cells. The expectation is that such mutations would ruin the input function altogether; instead, most of the 12 unique variants that were represented caused the system to respond in a different way to the input stimuli — that is, they behaved as pure AND or OR gates or as switches that responded to only one of the two inputs.

This tells us that the *lac* promoter is plastic to mutations, and indicates ways in which a gene

control region can evolve — not just by destroying its regulation but by altering it in potentially useful ways. A mathematical model was then constructed to account for the effect of such mutations; the model maps the phenotypes that certain types of mutant combination can and cannot reach, and therefore can be used to understand in more detail how mutations in certain binding sites lead to particular phenotypic effects.

While we wait to see whether the same conclusion can be extended to other regulatory systems, we can use this information to design more sophisticated artificial gene circuits, most of which are currently based on promoters that respond to a single input.

Tanita Casci

ORIGINAL RESEARCH PAPER Mayo, A. E. et al. Plasticity of the *cis*-regulatory input function of a gene. *PLoS Biol.* **4**, e45 (2006)

FURTHER READING Benner, S. A. & Sismour, A. M. Synthetic biology. *Nature Rev. Genet.* **6**, 533–543 (2005)

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