

Editorial

Gene regulation, evolvability and the limits of genomics

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Of the fundamental issues in biology that remain unresolved, one of the most prominent is that of the evolution of gene expression. Unlike proteins, in which conservation of function is largely reflected in conservation of primary sequence, conservation of function in the regulatory regions of genes seems to be maintained in the face of quite widely divergent primary sequence. Since the diversification of species depends much more on divergent gene expression than on divergent gene sequence (we famously share 95% of our genomic sequence with chimpanzees), the relationship of promoter structure to promoter function and the evolution of gene expression are a focus of considerable topical interest.

Earlier this year, we published a paper from Chan *et al.* [1] examining the relationship between conservation of gene expression and conservation of regulatory sequence in twenty tissues from three vertebrate species. They reported almost no conservation of associated noncoding sequence for genes with highly conserved expression patterns – a result that is consistent with accumulating evidence from other studies, discussed in the associated commentary from John Malone and Brian Oliver [2].

In this issue, Tirosh *et al.* [3] review recent studies in yeast aimed at identifying those properties of promoters that might account for the evolutionary divergence and the evolvability of gene expression, and focusing not on the primary sequence of regulatory regions but on their more general architectural properties and the relative contribution of regulatory DNA and the proteins that are required for its regulation.

The number of binding sites for regulatory proteins is larger in promoters of genes with divergent expression patterns, which does not seem hard to understand; and there are more bound nucleosomes, which is not so easy to understand (Tirosh *et al.* suggest more scope for regulation); and expression levels are noisier in genes in which they have diverged. But two of the conclusions reached by Tirosh *et al.* are particularly striking. The first is that divergence of expression patterns between different yeasts is associated with promoters that contain TATA boxes, a property generally associated with inducible

rather than constitutive gene expression (an important association first noted by Struhl and colleagues [4]). The second is that it is mutations in proteins and not in regulatory DNA that chiefly accounts for expression divergence – although it is important to note here that we do not know the identity of the proteins: the experiments simply ask whether in a yeast hybrid the pattern of gene expression travels with the DNA containing the gene, or with the DNA of the other parent – that is, in the classical terminology, whether the effect is in *cis* or in *trans*.

The predominance of *trans* effects is consistent with the intuitively reasonable idea, gaining general currency and rehearsed by Tirosh *et al.*, that the divergence and indeed the evolvability of gene expression is associated with the responsiveness of promoters to varying input – for example, from signals from the environment. This of course also fits neatly with the association of divergent expression patterns with inducible genes.

The mechanisms associating promoter architecture with expression evolvability remain unknown. But it seems clear that the information available from genomic DNA alone, no matter how ingeniously analyzed, is unlikely to provide the answer.

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