

Regulatory networks in evolution

Comparison of evolutionary adaptations and innovations illuminates the genetic basis for the development of animal forms. Gene networks that retain similar wiring diagrams in diverse and distantly related organisms point to the ways in which regulatory regions of the genome evolve. We may be close to being able to use comparative genomics to predict the evolvability of gene networks.

The evolution of development in animals and plants (evo–devo) is one area of interest to our new sister journal *Nature Ecology and Evolution* (<http://www.nature.com/natecolevol/>). Aspects of this field are certainly of interest to us too, as the scope of this journal centers on all aspects of analysis of regulatory variation—both within and between populations—and on the functional analysis of perturbed gene networks. Evo–devo engaging both of these strategic topics is growing because it is now possible to combine genomics, epigenomics, developmental genetics of model organisms and the comparative method.

Regulatory architecture does not readily identify itself. Previous strategies for identifying regulatory regions of genes, such as picking the nearest gene a certain distance from the element, get hit-and-miss results because they ignore the biology of distal elements. Now, Katherine Pollard and colleagues (p 488) offer an analytical approach providing a more accurate way to pair up putative enhancers with their respective promoter elements by taking into account local chromatin features of the intervening loop. Because enhancer elements often comprise flexibly arranged arrays of small redundant motifs recognized by transcription factors, they consequently evolve rapidly (*Nat. Genet.* **46**, 685–692, 2014; <http://dx.doi.org/10.1038/ng.3009>) and exhibit no necessary connection between their overall sequence conservation and the conservation of their function. On page 575, Douglas Epstein and colleagues used the overlapping expression patterns of enhancer-trap constructs in space and time in the developing forebrains of transgenic mice to identify *cis*-regulatory elements sharing transcription factors. For example, the SBE1 motif cluster and its associated transcription factors have a conserved function in establishing a Shh morphogen signaling center in both hemichordate and mouse, despite little extended sequence conservation or homology between the

developing anatomical regions. These findings, together with examples from three other ectodermal patterning centers conserved between hemichordates and vertebrates (*Nature* **483**, 289–294, 2012; <http://dx.doi.org/10.1038/nature10838>), show that innovations in vertebrate brain anatomy made use of preexisting and conserved transcriptional control networks rather than having their origins in the rewiring of regulatory architecture.

Most ambitious of all would be to understand the changes in regulation across entire genomes in the context of extreme morphological adaptation, such as that of the bat wing as it is adapted to flight. Using their *de novo* assembly of the vesper bat genome, Walter Eckalbar, Stephen Schlebusch and colleagues (p 528) compared primordial bat wing and hindlimb gene expression at three stages of embryonic development. Although much remains to be done in mouse models to investigate the multiple hypotheses this work generates, these developmental and evolutionary comparisons of gene expression patterns show up a range of interesting processes. These include the roles of morphogen regulatory networks, uncharacterized regulators (lncRNAs), coordination of morphogenetic pathways and even some innovations (new membrane musculature and gradients of bone mineralization).

As these and similar whole-genome comparisons of nonstandard model organisms allow us to move up from single-gene and single-network explanations for parts of developmental processes, so we will be able to compare networks within one organism as well as to compare retained networks across evolutionary time. We will then have access to the consequences of molecular evolution of the regulatory genome. In the modes of variation of regulatory elements, in changes to network architecture and in changes in internetwork coordination, we should be able to find some new and surprising biology and a better understanding of the diversity of animal forms. ■