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NEWS AND VIEWS

Chromatin regulators shape the genotype–phenotype map

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Whereas mechanistic developmental biology and evolutionary genetics largely proceeded independently from each other throughout most of the twentieth century, new discoveries and technologies have made it possible to revisit longstanding questions of how molecular mechanisms generate the phenotypic effects of alternative alleles. Pioneers such as Schmalhausen (1949) emphasized that phenotypic variation can often be surprisingly limited to both within and between species and proposed that the process of development and its genetic underpinnings are organized to allow a 'reserve of hereditary variability ' to accumulate within a species that can then be mobilized when conditions change . We are now in a position to dissect the molecular mechanisms that generate the apparent mismatch between extensive genetic and limited phenotypic variation. One important milestone was the discovery that knocking out the activity of the molecular chaperone Hsp90 results in an efflorescence of phenotypic variation due to the exposure of underlying genetic variation. The effects of new mutations are context dependent, and functional Hsp90 dramatically reduces these effects under normal conditions (Rutherford and Lindquist, 1998). Such genes that allow variation to accumulate without having an effect have been dubbed *capacitors* (Figure 1). In a recent article published in *Molecular Systems Biology*, Tirosh *et al* (2010) provide new evidence that chromatin regulators may also act as capacitors for gene expression.

Early proposals for explaining the maintenance of genetic variation within populations focused on external forces, e.g., balancing and purifying selection (Lewontin, 1974). Better data on how genetic variation is distributed within and between species and how genetic information is actuated to produce phenotypes made it possible to consider intrinsic factors. For instance, the redundancy of the genetic code provided an explicit internal mechanism for how the effects of genetic variation (at least on coding sequence) could be masked or generated. Kimura (1968), King and Jukes (1969) seized upon this and other functional data to support their claim that most genetic variation is selectively neutral or nearly so. Models of how metabolic flux is controlled along linear pathways showed why null alleles of metabolic enzymes tend to be recessive and therefore that network organization affects the neutrality of alleles (Kacser and Burns, 1981). One of the key insights of these papers was that genotypic variation is processed and filtered at multiple steps during the generation of a phenotype, such that its effects may be removed long before selection even has a chance to see it. There are more possible genotypes than phenotypes (Figure 1).

The discovery that molecular chaperones can buffer genetic variation led to an ongoing search for other classes of genes that act as capacitors. Tirosh *et al* (2010) use gene expression profiling in engineered strains of two species of yeast to show that chromatin regulators may have this role and mask the effects of genetic divergence between species. They reasoned that if chromatin regulators reduce the effects of allelic differences on gene expression, then deleting them should increase the divergence of gene expression levels between species. In order to test this hypothesis, they deleted eight different chromatin regulators and one transcription factor in two closely related species of yeast, *Saccharomyces cerevisiae* and *S. paradoxus*, which diverged about 10 Mya, but normally have similar expression patterns (Tirosh *et al*, 2009). When the same regulator was deleted in each species, genome-wide gene expression divergence systematically increased. A control experiment where 11 metabolic genes were deleted did not reveal such a systematic effect, implying that chromatin regulators are capacitors and that this is not an effect of all deletions—at least on a system-wide scale.

S. cerevisiae and *S. paradoxus* have the key property that they can breed and produce hybrids. This allowed Tirosh *et al* (2010) to ask whether the effects of the mutations that were revealed by the chromatin regulator knockouts are generally in *cis* (local) to the affected gene or in *trans*. Using allele-specific expression profiling in F1 hybrids, they showed that most of the increased divergence upon chromatin regulator deletion

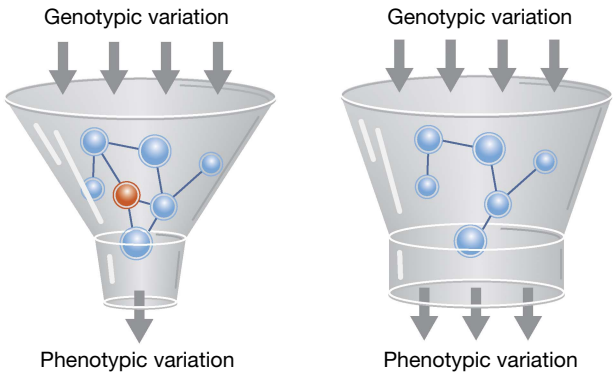

Figure 1 Physiological and developmental mechanisms reduce the spectrum of possible phenotypes that can be produced from a set of genotypes. Genes or nodes in the network that increase the phenotypic effects of mutations when removed are potential capacitors (orange node here).

could be traced to *trans* effects. This implies that chromatin regulators buffer expression variation by acting on components located upstream of the expressed genes themselves. This suggests that chromatin regulators may function as capacitors that prevent variation occurring at upstream locations from propagating downstream in the regulatory network.

The demonstration that specific molecules act generally to funnel pervasive genetic variation into a smaller spectrum of phenotypes (Rutherford and Lindquist, 1998; Tirosh *et al*, 2010) implies that the mapping between genotypic and phenotypic states might also evolve on microevolutionary timescales. The set of genotypes that can produce a particular phenotype might shrink or grow depending upon allelic variation at a chromatin regulator locus, although it is far from clear that selection can discriminate between alleles of capacitors based solely on their ability to buffer genetic variation. To clarify this point, we need to identify segregating alleles of these capacitors with different buffering abilities in natural populations and further explore the conditions that favor their fixation or elimination. The ability to measure heritability of noise in gene expression in natural strains of yeast opens this possibility (Ansel *et al*, 2008). Also left unresolved is whether chromatin regulators can buffer mutations that occur *de novo*. Indeed, the genetic differences that were tested using these two species have been sorted by billions of generations of natural selection. Finally, the molecular mechanisms by which chromatin regulators may buffer variation are unknown. The chaperone function of Hsp90 directly suggests a model, by which it can accommodate the accumulation of non-synonymous substitutions (Rutherford and Lindquist, 1998). As more capacitors are discovered (Levy and Siegal, 2008), both global and local, linking their molecular mechanisms of action to their buffering effects will be an important component in explaining how genotype is mapped to phenotype and in integrating developmental and evolutionary genetics.

Conflict of interest

The authors declare that they have no conflict of interest.

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