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Remodelling animal body plan, gene after gene

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Changes in Homeotic (*Hox*) genes' regulation have long been thought to drive the evolution of animal body plans. Direct genetic evidence of their evolutionary role has, however, remained limited. A new study reveals how several mutations distributed across a gene network mask the phenotypic effects of a *Hox* gene's evolution.

Hox genes have occupied a special place in the heart and the mind of developmental biologists, ever since Ed Lewis demonstrated their role in assigning fate to body segments of the genetic model *Drosophila melanogaster* [1]. The link between their function and animal morphology was substantiated by a key finding: their expression along the anterior-posterior (AP) embryonic axis [2, 3] prefigures the identity of each segment. Therefore, a change of *Hox* expression could mean a change of body plan [4].

The importance of *Hox* genes in defining animal body plan organization grew even bigger as they were studied outside of model organisms. First, with the realization that these transcription factor encoding genes have conserved functions in patterning the AP axis in all animals. Second, because variation in *Hox* expression patterns between species often correlates with body plan differences [4]. These observations suggested that changes in *Hox* gene regulation is a major driver of animal body plan evolution [5]. This notion was indirectly supported, in the wake of Ed Lewis' pioneering work, by experimental shifts of *Hox* gene expression along the AP body axis. Such shifts appear sufficient to change the suite of segment-specific morphological characteristics that define a segment's identity. Changing segmental identity means in effect to change the body plan [6].

In spite of the demonstration that shifting *Hox* gene expression can alter body plan organization, evidence showing that evolution of *Hox* gene regulation has directly contributed to morphological changes between species has remained surprisingly scarce [7]. In this issue of *Current Biology*, Liu et al. [8] address this problem by focussing on a difference in segmental identity, a change of abdominal pigmentation between two *Drosophila* species [9]. In *D. yakuba* males the last two posterior segments of the abdomen (A5 and A6) are darkly pigmented, while in *D. santomea*, this intense abdominal pigmentation has been lost [10] (Fig. 1). Liu et al. have examined the role of the *Hox* gene *Abdominal-B* (*Abd-B*) in this divergence, reasoning that *Abd-B* is required for male posterior abdominal pigmentation in the closely related species *D. melanogaster* [11]. Strikingly, they found that *Abd-B* expression pattern has changed between *D. yakuba* and *D. santomea* in line with their abdominal pigmentation. It is expressed in *D. yakuba* posterior segments during late pupal development, but not in A5 in *D. santomea*, which is not pigmented. The loss of *Abd-B* segmental expression therefore correlates with the loss of pigmentation in *D. santomea*.

Liu et al. first characterized the cis-regulatory element driving *Abd-B* expression in posterior abdominal segments of *D. yakuba*. Then, using Crispr-Cas9 mutagenesis, they deleted this element to eliminate *Abd-B* expression from A5 and A6 in *D. yakuba*. This prevented the formation

of dark pigmentation in these segments, stressing the essential role of *Abd-B* in this process. Furthermore, the authors found that the *D. santomea* counterpart of this *Abd-B* cis-regulatory element is inactive. Together, these results could have suggested that the evolutionary elimination of *Abd-B* expression from the posterior segments was an essential step to prevent pigment production in *D. santomea*. However, the effect of a mutation in one species is not always indicative of the genetic difference underlying the divergent phenotypes between species [12].

To directly examine the contribution of *Abd-B* expression change in pigmentation divergence, Liu et al. took advantage of the fact that *D. yakuba* and *D. santomea* can still hybridize. In the hybrid progeny, in which the *D. yakuba* *Abd-B* allele is expressed in A5 and A6, males develop some posterior pigmentation, indicating that the *D. yakuba* genes that govern abdominal pigmentation override their *D. santomea* counterparts. For this reason, Liu et al. decided to introgress *D. yakuba* *Abd-B* into *D. santomea*, to replace in the *D. santomea* genome *Abd-B* by its *D. yakuba* homolog. The *Hox*-centered view of body plan evolution predicts that an introgressed *D. yakuba* *Abd-B* allele would suffice to make the abdominal tip of *D. santomea* males dark. Surprisingly, the experiment told another story. The introgressed *D. santomea* males look as pale as their wild-type parents, although *Abd-B* is expressed in A5 and A6. In other words, restoring *Abd-B* expression in posterior segments of current-day *D. santomea* is not sufficient to restore the ancestral pigmentation pattern.

The difference between species hybrids and the *Abd-B* introgressed flies suggests additional changes between *D. yakuba* and *D. santomea*, presumably downstream of *Abd-B*. This idea is consistent with a previous genetic analysis revealing that four different genomic regions contribute to the pigmentation divergence [13]. Liu et al. identified five independent genes contained in these four genomic regions. One of these genes is *Abd-B* itself, as explained above. Three other genes, *yellow*, *tan* and *ebony*, are directly involved in pigmentation metabolism and were known for their role in the loss of pigmentation in *D. santomea* [14, 15]. In darkly pigmented species, the expression of these three genes in posterior segments is controlled by *Abd-B*. In *D. santomea*, by contrast, *Abd-B* appears to no longer govern these genes. It is unclear if they have lost their sensitivity to direct *Abd-B* inputs, or if, instead, they have become more sensitive to other regulators overriding *Abd-B*. A good candidate for this latter hypothesis is *pdm3*, the fifth gene contributing to the abdominal pigmentation divergence between *D. yakuba* and *D. santomea*, and a known repressor of pigmentation [16, 17].

With their meticulous study, Liu et al. have pieced together the genetics that explains the evolution of abdominal pigmentation in *D. santomea*. This transition involved a change in expression of a *Hox* gene, but also changes in the regulation of other genes, including among the targets of this *Hox* gene (Fig. 1). This is insightful in regard to body plan evolution, if one accepts that pigmentation pattern is one aspect of segment identity. A subtle change in body plan, as seen in *D. santomea*, results not from the sole change of *Hox* gene regulation, but from a series of mutations distributed across a gene network. The abdominal coloration of *D. yakuba* once evolved through new regulatory links between *Abd-B* and pigmentation genes. It was subsequently lost in *D. santomea* by cutting or silencing these regulatory links.

This sort of progressive gene network rewiring is likely to also explain more pronounced changes in segment morphology. In flies, the evolutionary transformation of wings of the third thoracic segment (T3) into flight balancing organs or halteres provides a textbook example of body plan evolution. The haltere fate is imposed by the *Hox* gene *Ubx*, which is specifically expressed in T3. In T2, where *Ubx* is absent, functional wings develop instead. During development, *Ubx* controls a very large set of target genes that collectively sculpt the appendage into an haltere rather than a wing [18, 19]. In butterflies, which have fully developed hindwings, *Ubx* function or expression are unchanged. Rather, the difference between flies and butterflies is better explained by numerous changes in the gene network governed by *Ubx* [18], much like the difference between *D. yakuba* and *D. santomea* in abdominal pigmentation is explained by changes in the gene network governed by *Abd-B*. In both cases, although over vastly different evolutionary time scales, it is the

accumulation of small effect changes in individual *Hox* gene targets that progressively generated body plan evolution.

One important question remains: why did *Abd-B* expression change in *D. santomea*, when cutting the regulatory links to its targets may have sufficed? It is conceivable that the change in *Abd-B* regulation is an aftermath of the loss of pigmentation, when the maintenance of expression in A5 is no longer a necessity. This scenario echoes a model in which evolutionary shifts of *Hox* gene expression do not drive but rather follow many evolutionary changes in *Hox* gene targets [20], therefore assuming gradual rather than abrupt body plan changes.

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Figure 1. The loss of abdominal pigmentation in *D. santomea* results from several evolutionary changes, distributed throughout the gene network controlled by the *Hox* gene *Abd-B*. In *D. yakuba*, *Abd-B* is expressed in the posterior abdominal segments (A5, A6) where it governs the formation of dark pigments by regulating pigmentation genes (left side). In *D. santomea*, *Abd-B* expression has disappeared from A5, which has also lost pigmentation (right side). The phenotypic effect of *Abd-B* evolution is masked by additional evolutionary changes (indicated by a lightning bolt) that make the pigmentation genes insensitive to *Abd-B* regulation.

Drosophila yakuba

Drosophila santomea

