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Morphing into Shape

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In 1917, British polymath D'Arcy Thompson proposed that the shapes of different organisms—say, a human and a chimpanzee—could be imagined as simple alterations of the same underlying pattern (1). Thompson famously demonstrated this idea by overlaying transformed Cartesian coordinates on drawings of related animals. This holistic view of organism shape inspired the British biologist Julian Huxley to point out that changes in shape can be thought of most simply as differences in the relative sizes of different body parts, thus reducing shape change to a more manageable problem (2). On page 63 of this issue, Crickmore and Mann (3) present a detailed analysis of the mechanisms controlling one striking difference in the relative size of two organs and uncover what may be a general mechanism of shape evolution.

In segmented organisms, such as flies and humans, similar structures that differ mainly in size and shape are produced in several locations along the main body axis. For example, humans produce arms and legs, largely using many of the same developmental mechanisms to pattern both organs. In fruit flies, two flying appendages, the wings and halteres (see the figure), also are built largely by shared developmental mechanisms. Halteres are delicate club-shaped organs that work like gyroscopes during flight. They evolved about 225 million years ago from more traditional-looking wings—such as the hind wings of butterflies—and have undergone a drastic reduction in size.

All of the differences between the wing and the haltere are determined by expression of a single “selector” gene called *Ultrabithorax* (*Ubx*), which is expressed in all cells of the developing haltere. When *Ubx* is experimentally removed from these cells, a fully formed wing grows instead of a haltere (4), revealing some of the underlying similarities between the two flight organs. *Ubx* somehow instructs other genes to alter the growth and development of haltere cells. In 1998, Weatherbee *et al.* (5) showed that *Ubx* regulates a battery of genes in the haltere, but until now we have not known precisely which genes are regulated to cause the greatest difference between the wing and the haltere: their fivefold difference in cell number in the adult.

Crickmore and Mann focused their attention on how *Ubx* influences the activity of *decapentaplegic* (*dpp*), a gene that is one of the key regulators of wing growth. Dpp protein is produced by cells that lie in a line that is several cells wide along the middle of both the wing and the haltere. The protein is then secreted from these cells and diffuses to neighboring cells. When the Dpp protein binds to its receptor, Thickveins (Tkv), two things happen. First, a signal is triggered within the cell and this signal is interpreted as “grow more.” Second, the Dpp protein is captured by the cell and eventually destroyed. Thus, Dpp protein diffuses away from the central cells and forms a gradient whose extent and steepness is controlled, at least in part, by the receptor Tkv.

Crickmore and Mann first noted that the width of the stripe of cells producing Dpp was narrower in the haltere than in the wing, and the level of expression per cell was also lower in the haltere. That is, less Dpp is produced in the haltere. Remarkably, they also found that the receptor Tkv is expressed in different patterns and amounts in the wing and in the haltere. In the central part

of the wing, *Tkv* expression is low, allowing the Dpp protein to move far from its source and creating two peaks of Dpp signaling on either side of the Dpp source. In the haltere, by contrast, all cells express high levels of *Tkv*, thus trapping Dpp close to the source and creating a narrow band of cells that respond to the Dpp signal. The result of all of this is that, relative to the haltere, more cells in the wing are exposed to the Dpp signal and they proliferate more than haltere cells.

Evolution appears to have hijacked an existing mechanism of growth control when flies evolved halteres. *Ubx* directs halteres to be smaller than wings by regulating multiple points in the Dpp pathway. It is remarkable that both the amount of the growth signal and the distance it is allowed to travel have come under the control of *Ubx*. Crickmore and Mann note that similar changes would provide an elegant mechanism for altering organ shape and size in different species. There is already evidence that changes in the expression of *Bmp4*, a relative of the *dpp* gene, in Darwin's finches are correlated with changes in the shape of the finches' beaks (6).

So how general is this mechanism? Molecules such as Dpp that transmit information through a field of cells in a graded manner are called morphogens. It is easy to imagine, given the data presented by Crickmore and Mann, that evolutionary alterations in the production and transport of morphogens through fields of cells could explain much of the geometric diversity observed by D'Arcy Thompson. Whether this is in fact the usual manner in which organ shape and overall shape evolve remains to be seen.

One particular difficulty is how this phenomenon scales to larger sizes. Morphogens tend to act over distances of tens of cells. It is difficult to imagine that tweaking a morphogen signal can lead to the differences between a fruit fly wing and a butterfly wing, or between a mouse and an elephant. Perhaps larger animals make larger organs by tinkering with morphogen gradients, or perhaps they generate new domains of morphogen activity. They may also have adopted an entirely different process that communicates with mechanisms controlling overall body size. There has recently been considerable progress in understanding how the insulin signaling pathway and other hormones (7,8) control body size in animals, but there is as yet little clarity about how morphogens and hormones intersect. It is nonetheless clear from the work of Crickmore and Mann that modification of the production and transport of morphogens may provide evolution with at least one powerful and flexible tool for altering organism shape.

References

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Figure 1. How is organ size controlled?

The *Ubx* gene is expressed in haltere cells, restricting the growth effect of the morphogen Dpp during development.