Last hideout of the unknown?

Scale and proportion: do the mechanisms of planar polarity also help determine the shape and size of animals?

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The mystery surrounding animal development is diminishing. We now understand much of how the DNA in the egg makes genes that build animals. We know how the body plan is elaborated from simple beginnings, and how the different types of cells are allocated and deployed. But there is one feature of animals for which we still have no explanation of any kind — yet it is so common that we pay it little attention. This is the characteristic and finely determined shape of animals — for instance, the three-dimensional space filled by a two-month-old okapi. A more familiar example is the fine sculpting of a face, such as the profile of your best friend. The mirror symmetry of the body, the trouble we have distinguishing identical twins and the way children resemble their parents should all remind us that these dimensions are prescribed genetically, written in the DNA sequence — but where and how? Here I conjecture, with only a little evidence, that the mechanisms that polarize cells within the plane of the epithelium could also help to sense dimension. An understanding of planar polarity might therefore help elucidate one of the deepest-remaining secrets of living things.

The important thing about growth is knowing when to stop. How do the cells in a growing bone of a mammal know when the final size has been reached? Moreover, both sides of an animal grow independently, but at identical rates — implying continuous action of the same control mechanisms on each side. In insects, the increase in size of the parts is spasmodic, being broken up into instars. At the start of the twentieth century, Harrison G. Dyar noted that the dimensions usually increase by the same proportion at each instar, giving a remarkably straight line on a log scale — again implying precise control. Some organs grow allometrically, that is, at a different rate to the rest. This precision suggests that there is a feedback from some measure of length in each main axis to every cell — for the decision to divide, not to divide or to die must be executed by each cell. The summed output of all those single-celled decisions in an organ will, in two or even three dimensions, determine its shape and size throughout growth and when it stops growing.

Any comparison between species raises the question of what is responsible for their different anatomies. I would guess that the main cause of evolution of shape is not the changing of protein sequences one into another. For example, it does not occur simply because proteins such as haemoglobin differ slightly in sequence between man and mouse. Indeed, I suspect that if one were to take human proteins, one by one, and swap them with the homologous proteins in a mouse, most would do their job well. As increased numbers of proteins were substituted, I do not think that the result would be an increasingly human-looking mouse. This would mean that the anatomical differences between a human and a mouse would have to be sought elsewhere in the genome, in whatever control sequences are responsible for the length of the tail or the squeakiness of the larynx. Poodles and rottweilers, as well as the diverse shapes and sizes of beetles, illustrate how freely dimensions can be adjusted — by human or natural selection.

Family resemblance: the shape and dimensions of our faces are prescribed in our genome.

Dimension in one axis could be controlled by a monotonic gradient. If the limits of the gradient were fixed, then, as the axis grows longer, the gradient would become less steep across every cell — this could be how overall dimension is conveyed to each cell. For example, in the *Drosophila* abdomen, there are at least two gradient systems. One is an archetypal morphogen, the Hedgehog protein, which spreads outwards from a source. Its concentration fixes the pattern of cell types and the gradient of cell affinity. The other, the less well understood gradient system, specifies planar polarity and seems to depend on intercellular bridges made by cadherin molecules. This polarity gradient might not decay with distance and could be of constant declination.

I offer three arguments that the polarity gradient, and not the morphogen gradient, specifies dimension. First, morphogen gradients do not seem to operate consistently over a growing field — as the axis elongates, some cells can become too remote from the source to be patterned. Large fields, such as developing butterfly wings, solve this problem by intercalating secondary morphogen sources to fill in the gaps. In the case of the *Drosophila* abdomen, regions far from the source are polarized normally and reach the right size even when rendered blind to Hedgehog — arguing that in this case Hedgehog is not directly responsible for either polarity or dimension. The second argument is that clones of cells that lack the polarity cadherins not only have defects in polarity, but also grow excessively, suggesting that these cadherins are a link between planar polarity and growth. The third argument is one of mechanism. A cell in an epithelial sheet may resemble an amoeba of *Dictyostelium* that is becoming polarized by a gradient of cyclic AMP. The amoeba compares the amount of cyclic AMP reaching the periphery of the cell and moves up the gradient of concentration. Similarly, in a sheet of cells, each one could monitor its plasma membrane to detect the gradient and to read the vector that specifies its polarity. Could the cell also measure the amount of the difference across itself? If so, could this comparison give it information about dimension, and perhaps tell it when to stop dividing? ■

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FURTHER READING

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