News & views

Evolution

A radical body-plan makeover explained

Thurston Lacalli

Echinoderms such as starfish are unusual for their five-fold body symmetry. Maps of gene-expression patterns show how this body plan was acquired, and that the genes specifying head structures do the heavy lifting. **See p.555**

Starfish and sea urchins belong to a group of marine invertebrates known as echinoderms, which stand out among other animals because of their unusual body plan. Most animal phyla are part of the group Bilateria, united by having bilateral symmetry, a head and a tail end (anterior–posterior axis) and opposing dorsal and ventral surfaces, corresponding to the back and abdomen. Echinoderms are bilaterians, but are something of an outlier because they replaced this basic bilaterian body plan with one in which five identical body parts radiate out from a central mouth (Fig. 1). On page 555, Formery *et al.*[1] reveal how echinoderms evolved this peculiar five-fold symmetry.

The earliest-known echinoderm fossils show evolutionary experimentation with other symmetries[2–4], but there is no consensus regarding the fate of the principal bilaterian body axis: is it gone, was it duplicated or was it otherwise reconfigured? The question has puzzled zoologists since the golden age of comparative anatomy in the nineteenth century. It has been particularly vexing because echinoderms are, along with hemichordates (acorn worms and their kin), among humanity's closest invertebrate relatives[5,6].

These issues are now largely resolved in the study by Formery and colleagues. The authors' focus is molecular rather than anatomical, and involves mapping the expression patterns of developmentally important genes across the body axes of the bat star (*Patiria miniata*). This approach works because expression patterns of this kind are more conserved across phyla than are anatomical structures[7]. For *P. miniata*, it is the genes involved in specifying head structures that tell the evolutionary story, which is a surprising one with implications for zoologists' understanding of echinoderms and their evolution along a path so strikingly different from our own. Hemichordates feature prominently in this story too, because they provide the best model for discriminating between the different subdomains in the head (or its counterpart), whether for vertebrates or for echinoderms.

The authors investigated 36 *P. miniata* genes, 20 of which were specific to anterior (upper), middle and caudal (lower) head regions, and that correspond to different anterior domains in hemichordates – parts of the proboscis and collar. When mapped to the body of *P. miniata* juveniles, these genes were expressed in concentric domains on the mouth-bearing undersurface of the body. The most-anterior genes were expressed closest to the mouth and to the centre of each of the five 'rays' of the star, along radial domains (ambulacra) that extend from the mouth (Fig. 1). More-caudal genes were expressed in the fringe of tube feet that surround the ambulacra. By contrast, known markers for trunk structures, including all but the most anterior of the Hox family of genes, were expressed only in internal tissues rather than on the surface.

The answer to where the anterior–posterior axis is therefore comes in two parts. First, only the anterior part of the axis, which specifies head-related structures, is represented on the body surface. Second, the axis maps across each ambulacrum at every point along its length, going from the anterior at the midline to the beginnings of the trunk at the margins. By contrast, the remainder of the body surface does not seem to be an active participant in patterning the body. This model has been confirmed only in starfish, but there is no reason to suppose that it will not apply to other echinoderms.

Although a slight oversimplification, the

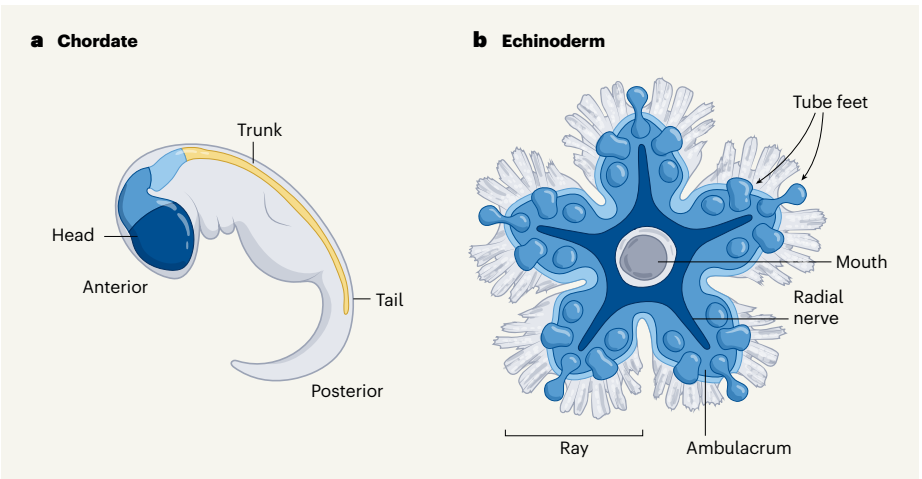

Figure 1 | Gene-expression patterns reveal the basis of the five-fold symmetry of the echinoderm body plan. **a**, In most animals, including chordates such as humans, the expression of genes that define the body plan during development is patterned along the anterior–posterior (A–P) axis going from head to tail. Blue and yellow represent different gene-expression patterns in the chordate nervous system. **b**, Echinoderms such as this juvenile bat star (*Patiria miniata*, shown here from the undersurface) have evolved a different body plan consisting of five identical rays emanating from a central mouth. Formery *et al.*[1] show that the A–P axis has been radically transformed in *P. miniata*. Genes specifying more-anterior structures are expressed along the midline of each ray where the radial nerve lies, and more-posterior genes are expressed towards the tube feet at the margin of each ambulacrum (blues corresponding to those in **a**). Genes that specify the trunk (yellow in **a**) in chordates have been lost from the body surface in echindoderms, along with the trunk as an identifiable anatomical structure.

findings suggest that one could think of the body of a starfish (at least in terms of the anterior–posterior identity of its surface tissues) as a disembodied head walking about the sea floor on its lips — the lips having sprouted a fringe of tube feet, co-opted from their original function of sorting food particles, to do the walking. A more accurate characterization would be that a neurogenic domain — a region that gives rise to the nervous system, a bit of ancestral forehead in this case — has grown to encircle the mouth to produce nerves. Meanwhile, tissue that is fated to form the region below the mouth has expanded forward around the margin of the neurogenic domain to produce the tube feet. This is truly a radical transformation of the ancestral bilaterian body plan. Knowing how it was done means that we now have a much firmer foundation for interpreting early echinoderm fossils, and a better understanding of how the regions of our own brain compare with their echinoderm counterparts.

In a broader context, the *P. miniata* data provide a striking example of a trend in echinoderms, in which the tissue layers become decoupled during development and are patterned separately[8,9]. In principle, such decoupling should allow the layers greater freedom to evolve independently in innovative ways. Yet, the more common strategy across phyla, in insects and other arthropods for example, is to have a point-by-point correspondence between developmental events occurring in tissues on the body surface and those deeper within. The advantage of one strategy over another is still a puzzle, as is the role of chance and circumstance — evolutionary contingency — in producing such different outcomes[10].

There is also then the question of why, with this loss of correspondence between tissues, echinoderms have lost the trunk as an identifiable structure. One answer is that the trunk of ancestral deuterostomes (the larger phyletic grouping to which echinoderms, hemichordates and chordates belong) might not have been especially useful as a locomotory device in the face of the increasing levels of predation characterizing the explosion in animal diversity that happened during the Cambrian period some 530 million years ago[11]. In contrast to echinoderms, the chordate ancestors of humans responded to that challenge by vastly improving their swimming efficiency, through the addition of a new set of muscles derived from blocks of embryonic tissue known as somites — structures that have no obvious counterpart in other deuterostomes. We lack sufficient knowledge of the shared common ancestor to understand what predisposed chordates to take this step, but it clearly opened up new habitats and adaptive possibilities.

Although the common ancestor from which the three deuterostome phyla evolved is elusive, there are Cambrian fossils that might be phylogenetically close, for example small tentacle-bearing animals such as *Herpetogaster*[12]. However, if the initial split in the main deuterostome lineages happened before the Cambrian explosion (as is probably the case), the paucity of convincing bilaterian body fossils from that period leaves us relying on what can be learned from living taxa. Any insight is then useful so long as it tells us something about the prevailing conditions at the time of the divergence, the developmental constraints that the organisms might have faced and the molecular and developmental mechanisms that were available to help them to overcome those constraints. This is what makes the work by Formery *et al.* so informative, beyond even what it says of echinoderms themselves.

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Virology

Anti-COVID drug accelerates viral evolution

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Molnupiravir, an antiviral drug used to treat COVID-19, induces numerous mutations in the SARS-CoV-2 genome that can increase the rate at which the virus evolves — yielding viral variants that might survive and be passed on. **See p.594**

Drugs are potent weapons against viral pathogens. During the early stages of the COVID-19 pandemic, there were intensive efforts to discover and implement antiviral drugs that could treat SARS-CoV-2 infections, either by reducing the intensity of symptoms or by shortening the duration of infection. One of the drugs identified as part of that work was molnupiravir. On page 594, Sanderson *et al.*[1]

"The rate of viral evolution could considerably exceed what is seen for standard antiviral drugs."

provide the most convincing evidence yet that molnupiravir-induced mutations in the SARS-CoV-2 genome can lead to new transmissible viral variants. Although there is no reason to think that any SARS-CoV-2 variant arose as a result of treatment with molnupiravir, public-health authorities should exercise caution when considering the therapeutic use of this drug and others that work in a similar way.

Most successful antiviral drugs, including those used to treat infections with HIV-1, hepatitis C and influenza A, work by selectively binding to a viral protein and thereby interfering with some key step in the viral replication cycle. Molnupiravir and other drugs that operate through a mechanism known as mutational error catastrophe are unusual because their intended function is simply to reduce the accuracy with which viruses copy their genomes. In theory, the drug-induced accumulation of numerous copying errors should yield viruses that are no longer viable — that is, they are unable to infect new cells, sustain replication or transmit to other hosts. But there is a danger that, instead of helping to control infection, drugs such as molnupiravir could occasionally yield heavily mutated yet viable viral variants. This is precisely what Sanderson *et al.* have found.

Knowing that molnupiravir almost always causes mutations of two particular types, Sanderson and colleagues developed a genomic 'fingerprinting' technique to scan millions of SARS-CoV-2 genome sequences for telltale signs of molnupiravir-induced mutations. Their analysis showed that thousands of viruses with many mutations — sometimes