problem of crystallographic disorder: X-ray crystal structures represent the average positions of all the atoms in a crystal, which complicates the interpretation of structures if any of the atoms are mobile, whereas HRTEM does not have this problem because it simply produces 'snapshots' of single POM complexes. It should be noted that the early steps of nuclear-fuel recycling remove most actinyl ions, minimizing the possibility that such ions will compete with the americyl ion for binding to the POM, should Zhang and colleagues' separation process be implemented by the nuclear industry.

The reported POM does not yet separate americium from lanthanides as well as does another method[9] described last year by researchers from the same group as Zhang *et al.*, in which an organic system was used to oxidize americium to the +V oxidation state. Nevertheless, the new findings are important for several reasons. They demonstrate that POMs have great promise for the selective binding of various radioactive metals in different oxidation states, and offer flexibility in how they can be used for physical separations. They show that the separations could be done in the absence of organic ligands or solvents that can degrade in the presence of these highly radioactive elements, simplifying and increasing the safety of the processes. And finally, the X-ray structure of the AmO_2^{2+}–POM complex provides useful information to aid the design of POMs that are even more selective for binding to the americyl ion.

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Evolution

Genome reveals how the skate got its wings

Chris Amemiya

Genome sequencing, combined with methods for deducing how genomic regions interact, have now provided insight into how the wings that give skates and rays their characteristic shapes evolved more than 200 million years ago. **See p.495**

Evolution involves the selection of particular traits, and these frequently arise during embryonic development. This interplay between evolution and development (known as evo-devo) was first recognized by Charles Darwin[1], but, in the past few years, evolutionary research has been buoyed by remarkable advances in molecular biology and genomics. On page 495, Marlétaz *et al.*[2] report the genome sequence of a fish known as the little skate (*Leucoraja erinacea*). The authors used an armamentarium of sequencing and developmental-biology tools to analyse how skates diverged from their closest relatives, sharks, and how their unusual pectoral fins evolved.

Skates and rays together make up the batoids — cartilaginous fishes characterized by wing-like pectoral fins that extend from their heads, resulting in a flattened body shape (Fig. 1). The evolution of these modified fins gave batoids different locomotor abilities from those of sharks, and enabled them to adapt to life on the sea floor. It has not been known how expanded pectoral fins emerged, although there is some evidence[3] for the involvement of a rapidly expanding 'growth zone' in the anterior part of the pectoral fin (the section closest to the head), which produces the unique fin shape during embryonic development.

Marlétaz and colleagues chose the little skate for their investigation into the evolution of batoid wings because it is one of the few batoid species for which embryos can be readily obtained. The team sequenced the fish's genome using a bevy of methods. One of the these, Hi-C, can reveal regions of the chromosome that do not lie adjacent to one another, but that interact through the formation of chromosome loops. The authors used Hi-C to analyse DNA from developing pectoral fins, capturing fragments of chromosomes that were in close proximity. These fragments then served as anchors that enabled the researchers to produce assemblies (in which individual stretches of sequence are arranged in the correct order) that were the length of entire chromosomes.

The authors also used their Hi-C data set to identify topologically associating domains

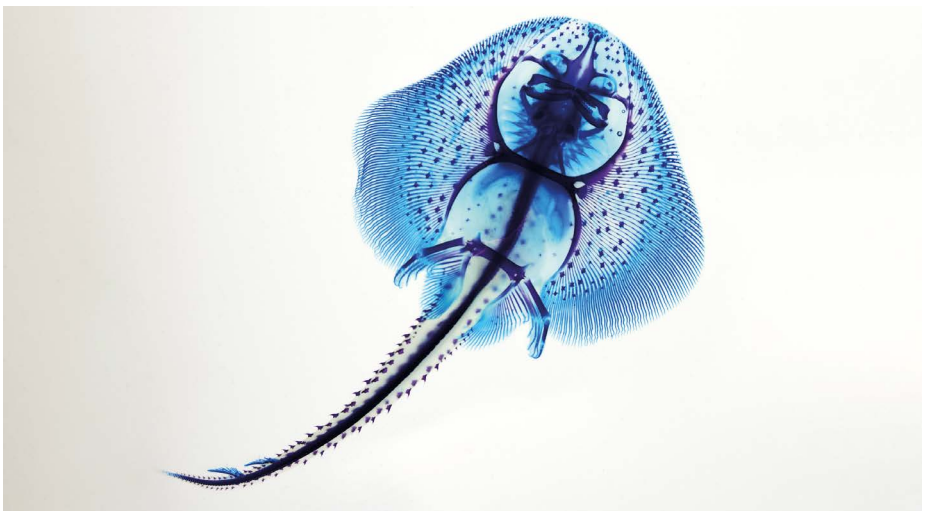

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Figure 1 | The little skate skeleton. Marlétaz *et al.*[2] sequenced the genome of the little skate (*Leucoraja erinacea*), and analysed the genetic changes that led to the evolution of the unusual wing-shaped pectoral fins that extend from either side of its head.

(TADs) — chromosomal regions in which genes and the regulatory sequences that control their activity (called promoters and enhancers) interact regularly, thus modulating gene expression. The team compared the skate genome with those of several other vertebrates, and found that, during the little skate's evolution, genome rearrangements had altered the structure of TADs that encompassed genes involved in a cell-signalling system known as the planar cell polarity (PCP) pathway.

The PCP pathway emerged early in animal evolution, and is known[4] to drive the establishment of cell shape and orientation — including in flattened sheets of cells — during development. However, its involvement in skate-fin development had not previously been described. Marlétaz and colleagues confirmed, using several experimental approaches, that the PCP pathway is involved in development and expansion of the skate's anterior pectoral fins. For instance, they showed that the PCP gene *Prickle1* is expressed to a greater degree in the anterior portion of the pectoral fin than in the posterior portion. Addition of a PCP-pathway inhibitor to the water in which young skates were being kept, or implantation of inhibitor-soaked beads directly into the pectoral fins, led to changes in fin development in the anterior region. The authors also corroborated the involvement of this pathway using a modified version of Hi-C known as HiChIP (which detects chromosome looping that participates specifically in gene regulation).

The involvement of PCP in skate-wing development was unexpected, but might have been predicted, because the way in which the flattened pectoral fin grows and expands is reminiscent of the development of other cell sheets regulated by the PCP pathway, such as fly wings[4]. Notably, the authors found scant *Prickle1* expression in the embryonic pectoral fin of the chain catshark (*Scyliorhinus retifer*), which, unlike the batoids, does not undergo an anterior expansion. This further supports the idea that the skate-specific expression pattern of *Prickle1* contributes to the wing-like fin.

Finally, Marlétaz *et al.* examined open chromatin — regions of the genome in which DNA is loosely packaged and so available for transcription factors to bind to genes and so modulate gene expression. Analysis of the open chromatin regions associated with genes that were differentially upregulated or downregulated in the anterior and posterior pectoral fin identified an enhancer involved in the regulation of several *HoxA* genes in the anterior fin. Genes of the *HoxA* cluster direct development of the body plan and limbs in all vertebrates[5]. Their divergent expression in the anterior pectoral fins, driven by the skate *HoxA* enhancer, probably contributes to expansion of this extra growth zone in the batoid wing.

Taken together, Marlétaz and colleagues' results support the idea that the anterior region of the developing skate pectoral fins is under different genetic control from that of the posterior region. Their work suggests that genomic events in the ancestor of the batoids might have facilitated the emergence of this evolutionary novelty.

There is much to celebrate in this paper. The authors have generated data resources for the little-skate genome, and have used these to address an evolutionary conundrum. Their use of TADs and TAD structure to make inferences about the relationship between evolution and development is especially exciting, because it provides a means of identifying key genomic changes that occurred deep in evolutionary time. However, caution should be exercised when interpreting these complex sequence-based data sets[6]. Moreover, the findings still need to be validated using conventional developmental-biology approaches, because the magnitude of a change does not necessarily reflect its importance — small mutations can have large effects on gene regulation, whereas bigger changes can be of little consequence.

The approaches used by Marlétaz and colleagues can also be adopted to address other evo-devo questions in batoids. For instance, what major genetic and structural changes led to the evolution of walking-type behaviour in skates[7], or oscillatory locomotion (a type of underwater flight suited to life in the open sea) in a subset of batoids, including manta rays and bat rays[8]? A combination of these approaches, alongside gene-editing techniques such as CRISPR and single-cell analyses, will enable many other fascinating natural-history stories to be investigated.

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Cancer

Viral agent of genomic instability

Lori Frappier

A protein from Epstein–Barr virus called EBNA1 has been shown to bind to and break human chromosome 11, producing instability in the genome that might cause a predisposition to cancer. **See p.504**

Epstein–Barr virus (EBV) is a common herpesvirus that is also associated with several types of cancer, including lymphomas, nasopharyngeal carcinomas and gastric carcinomas[1]. How exactly the virus affects the development of these cancers is unclear, but tumour cells are known to be derived from infected cells that express a small subset of EBV proteins. In fact, the only viral protein that is expressed in all types of EBV-related cancer is Epstein–Barr nuclear antigen 1 (EBNA1), which binds to specific sequences in the viral DNA, allowing it to persist and replicate. The possibility that this protein contributes directly to cancer has long been proposed and disputed[2]. Li *et al.*[3] suggest on page 504 how it might do so — by binding to a specific region on human chromosome 11 and triggering its breakage, thereby inducing genomic instability.

EBV persists in human cells for a lifetime, and promotes cell proliferation in a form of infection referred to as latency. EBNA1 is expressed in the dividing cells, and binds to multiple repeated sequences in the EBV genome. Biochemical and structural studies have defined how the DNA-binding domain of EBNA1 interacts with an 18-base-pair (bp) palindromic DNA sequence[4–6]. The ability of this protein to bind to viral DNA has prompted investigations into whether it also recognizes specific sequences in host DNA, and previous studies of EBV-infected immune cells called lymphocytes have identified numerous possible target sequences, but with no clear consensus[7]. Among these is a cluster of high-affinity EBNA1-binding sites on chromosome 11,