Abstractions

LAST AUTHOR

Knowledge about the earliest stages of vertebrate evolution draws heavily on information from 500-million-year-old fossils of early chordates — an animal group that includes vertebrates and their closest relatives. Lacking bones, teeth or shells, these ancient soft-bodied animals left behind a sparse record, and there are few well-preserved examples. This has made it hard to interpret their anatomy and evolutionary significance. Now, Mark Purnell and his colleagues at the University of Leicester, UK, have learned more about the way such organisms decay and how this may affect their proper placement in the evolutionary tree (see page 797). Purnell tells *Nature* more.

What did you use as a proxy for such ancient animals?

We studied the two modern-day chordates thought to most closely resemble their early relatives. Amphioxus are finless fish-like creatures; ammocoetes are larvae of lampreys, jawless fish that resemble eels. The amphioxus came from the Mediterranean, the ammocoetes from Yorkshire, UK.

How did you do the experiment?

We wanted to record how particular anatomical characteristics of chordates change or disappear during decomposition. So we sealed the specimens in clear plastic containers filled with sea water or fresh water, depending on where they had lived, and placed them in temperature-controlled cabinets. Then we left them to rot. To say it was unsavoury and unpleasantly pungent is an understatement.

How did you record the decay?

We photographed and dissected the organisms to see which characteristics endured. We expected the animals to lose features over time, but what surprised us was that the decay followed a very clear pattern. Those characteristics most useful for correct phylogenetic ordering were the first to disappear. In other words, the characteristics that decayed first were the ones that were unique to amphioxus or to ammocoetes.

Do your findings have implications for the field of evolutionary biology?

Yes. They confirm that we can't assume any fossil has been unaffected by decay. Fossils that seem to have only decay-resistant characteristics and seem to be primitive must be viewed carefully. It could be that they're actually the badly decomposed remains of a more complex organism. Fossil soft-bodied animals are undoubtedly important, but we may have to accept that there are uncertainties about the anatomy and placement of some. ■

MAKING THE PAPER

Constantin Polychronakos & Michael German

Projects converge on gene central to formation of insulin-producing cells.

Constantin Polychronakos (left) and Michael German.

Two independent projects in different countries and with very different subjects came to the same conclusion at around the same time. Both pinpoint a gene as having a crucial role in the formation of the insulin-producing β-cells of the pancreas — the cells that are defective in some forms of diabetes.

Although there are various causes, diabetes ultimately results from insulin dysregulation. In one of the two most common forms of the disease, type 1 diabetes, the immune system attacks the pancreatic β-cells, progressively destroying them. Patients are treated with insulin injections, but scientists hope one day to be able to produce β-cells in the lab and then introduce these into patients to replace faulty or damaged cells.

Constantin Polychronakos, a geneticist at McGill University in Montreal, Canada, has a long-standing interest in the genes that predispose people to type 1 diabetes. But in 2004, during clinical rounds as a paediatric endocrinologist, he was intrigued by a rare form of neonatal diabetes in two siblings. As he described in a publication that year, each child's pancreas completely lacked insulin-producing β-cells, as though the body had not had the proper instructions for making them.

"Because the patients were siblings, had exactly the same disease and had parents who were second cousins, it seemed likely that the disease was caused by a mutation in a single gene inherited from both parents and derived from the same great-grandparent," says Polychronakos. To begin the hunt for this mutation, Polychronakos and his team used a technique called homozygosity mapping. Every child inherits one half of each chromosome pair from each parent. Depending on how closely related the parents are, some regions in each chromosome pair will be identical, or homozygous. "In children whose parents are second cousins, 3% of the genome is homozygous," says Polychronakos. He reasoned that the mutated gene inherited by the siblings with neonatal diabetes was almost certain to reside in one of those homozygous regions.

Polychronakos and his colleagues went on to identify the regions of homozygosity in the two siblings' genomes, and in that of another child who had since been identified with the same disease in the United Kingdom. This allowed them to narrow down the list of candidate genes to about 200. "That is a heck of a lot of genes," Polychronakos admits. "But with current sequencing technologies it was feasible to sequence them all to find the mutation."

> **"We now have a more complete picture of how to make a normal, mature β-cell."**

At around that time, in September 2007, Polychronakos received an e-mail out of the blue from Michael German, a diabetes researcher at the University of California, San Francisco. German's lab was examining the function of a mouse gene called *Rfx6* that he had a hunch might be responsible for the unusual condition of the two siblings that Polychronakos had described.

German's lab was trying to define the mechanisms by which insulin-producing β-cells develop. One gene, neurogenin 3, was known to 'switch on' several other genes that then worked together to make a β-cell. Some of those had already been isolated, and German's group determined that *Rfx6* was part of the neurogenin 3 network. But *Rfx6* stood out: "It is expressed early in the development of the embryo and specifically in the endoderm, the part of the embryo that forms the gut," says German. "But later in development, *Rfx6* expression becomes restricted to the β-cells of the pancreas. And it is never expressed in the brain, as are all the other genes regulated by neurogenin 3."

When he contacted Polychronakos, German's lab had just knocked out *Rfx6* in mice, and the team was anxiously awaiting the results, which "took much longer than they should have", laughs German. "At one point we started thinking the gene was cursed because everything that could have gone wrong with those mice went wrong."

But perseverance paid off, and in the end the researchers got their knockout mice, which bore a striking resemblance to the patients Polychronakos had described. In the meantime, Polychronakos's gene-sequencing results had come through, confirming that the faulty gene in his patients was indeed the human counterpart of *Rfx6* (see page 775).

Experiments in mice indicate that *Rfx6* is one of the earliest genes to be turned on by neurogenin 3 and may thus provide a valuable tool in efforts to generate β-cells for patients with diabetes. "We now have a more complete picture of how to make a normal, mature β-cell," says German. ■

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