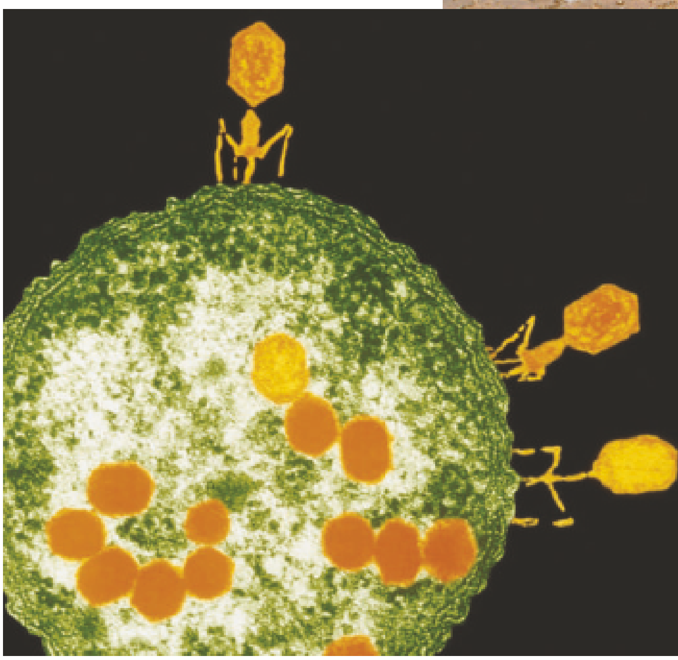
Hot springs give a glimpse of the wild diversity of viruses. But did these tiny experimenters stumble across DNA in their bid to invade cells?

BASE INVADERS

Could viruses have invented DNA as a way to sneak into cells? **John Whitfield** investigates.



What with the threat of bird flu, the reality of HIV, and the general unseemliness of having one's cells pressed into labour on behalf of something alien and microscopic, it is small wonder that people don't much like viruses. But it's possible that we may actually have something to thank the little parasites for. They may have been the first creatures to find a use for DNA, a discovery that set life on the road to its current rich complexity.

The origin of the double helix is a more complicated issue than it might at first seem. DNA's ubiquity — all cells use it to store their genomes — suggests it has been around since the earliest days of life, but when exactly did the double spiral of bases first appear? Some think it was after cells and proteins had been around for a while. Others say DNA showed up before cell membranes had even been invented[1]. The fact that different sorts of cell make and copy the molecule in very different ways has led others to suggest that the charms of the double helix might have been discovered more than once[2]. And all these ideas have drawbacks. "To my knowledge, up to now there has been no convincing story of how DNA originated," says evolutionary biologist Patrick Forterre of the University of Paris-Sud, Orsay.

Forterre claims to have a solution. Viruses, he thinks, invented DNA as a way around the defences of the cells they infected[3]. Little more than packets of genetic material, viruses are notoriously adept at avoiding detection, as influenza's annual self-reinvention attests. Forterre argues that viruses were up to similar tricks when life was young, and that DNA was one of their innovations.

To some researchers the idea is an appealing way to fill in a chunk of the DNA puzzle. Furthermore, the hypothesis should be testable through genomic studies and even lab experiments. But whether or not it pans out, Forterre's idea reflects an emerging consensus that viruses' diversity, mobility and capacity for rapid change has made them major players in some of the most important moments in life's evolution.

Small world

Most researchers think that before there was DNA, life stored its information in RNA, the double helix's more versatile chemical cousin. RNA is a slender, flexible molecule, usually made as a single strand. RNA molecules can contort in ways that allow them to catalyse chemical reactions, including in some cases their own replication. It is possible to imagine an 'RNA world' where the molecule does almost everything — catalysing reactions and replications that would today be catalysed by proteins, and storing information that would now be stored in DNA. It is not possible to imagine DNA, a rigid, double-stranded rod that can be replicated only with the help of a protein, operating as a one-molecule band in the same way. That's one reason for thinking it came along later, after complex proteins had been added to the RNA world.

Once DNA did arise, it would have had several advantages as genetic material. DNA's skeleton is more chemically stable than RNA. This stability allows DNA genomes to be longer, and so allows organisms to become more complex. But, as Forterre points out, the beneficial chemical property cannot explain why DNA appeared in the first place. Natural selection has no foresight; no innovator could acquire DNA on the basis that it would later be helpful in the expansion of its genome. "That would be like saying that dinosaurs evolved feathers because they knew they were going to turn into birds," says Forterre.

Instead, he thinks that DNA's original selective edge was that it allowed viruses to avoid their host's defences. Many cells repel invaders by degrading their genetic material. But enzymes that had evolved to break down RNA would have ignored DNA.

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"A virus that invented DNA would have a tremendous advantage in overcoming cellular defences," agrees Malcolm White, a proteomics researcher at the University of St Andrews, UK. Forterre's hypothesis "fits with a lot of the clues that are scattered through genomes and phylogenies", he adds.

Insider traders

Two main lines of evidence point to viruses as likely genetic innovators, says Forterre. One is the diversity of genetic systems in contemporary viruses, which suggests an evolutionary tendency toward reinvention. Viruses have genomes made from double- and single-stranded DNA, double- and single-stranded RNA, and even DNA in which the chemical base uracil — also used in RNA — replaces the usual thymine. The genome can be carried on a single string, on a closed loop, or as a set of fragments. Many of these changes are thought to have occurred to help viruses avoid their host's defences.

In fact, biologists believe they are only just beginning to fathom the extent of this diversity. "We don't know much about the viruses of the world," says Philip Bell, a molecular biologist at Macqaurie University in Sydney, Australia, who has argued that the nuclei found in complex cells are also descended from viruses[4]. Many of the viruses now being found in hot springs, for instance, feature unusual shapes — including spindles, rods, filaments and droplets — as well as genes with no known counterparts in other organisms[5].

The other line of evidence rests on relations among the genes used for DNA processing. There are three domains of cellular life: archaea, bacteria, and eukaryotes (the group containing plants and animals). All three share similar genes for turning genetic information into protein, and a similar enzyme for converting the components of RNA into those of DNA. This strongly suggests that these genes arose before the domains went their separate ways, probably in the RNA world.

But the similarities break down for DNA helicases and polymerases — the enzymes that unwind the DNA double helix and copy each strand. Although the archaeal and eukaryotic versions of these genes are similar, the bacterial versions are radically different from both, suggesting that perhaps these DNA replication systems evolved independently. What's more, the DNA polymerases of eukaryotes and bacteria are more closely related to similar enzymes found in viruses than they are to each other. This all implies to Forterre that the ability to copy DNA molecules did not originate with cells, but with their parasites.

In Forterre's scenario, the RNA genes in a cell infected with a DNA virus migrated to the new, more stable format over time with the help of a reverse transcriptase — an enzyme that makes DNA copies of RNA genes. Viruses could be expected to contain such enzymes, as they are so helpful for replication or for pinching useful genes from a host. Once the DNA genome became a complete warehouse of cellular genes, the original RNA chromosomes would be redundant. The process happened more than once, which explains the different DNA handling systems.

P. FORTERRE

Anthony Poole, an evolutionary biologist at Stockholm University, Sweden, finds the idea intriguing. The hypothesis fits with much of the evidence from viral biology and gene trees, he says. "It's very well thought out. I like it a lot."

At the same time, Poole warns, the evidence is ambiguous. For instance, although viruses and cells swap genes with alacrity, it can be difficult to work out which genome gave birth to an innovation, and which imported it. "Phylogenies suggest a relationship between viral and cellular sequences. The problem is we don't know the order things happened in — viruses could derive from cellular lineages," he says.

Nor is everyone persuaded by Forterre's idea. Bill Martin, an evolutionary biologist at the University of Düsseldorf in Germany, says he agrees that the evidence points to DNA arising more than once, and that reverse transcriptase was probably involved in the transition from RNA to DNA. But he doubts that DNA's original selective advantage lay in infection. "It's completely off-target," says Martin. "The simple chemical stability of DNA is the main point."

Viral marketing

Forterre advocates gathering gene sequences from a greater diversity of viruses to seek descendants of the lineage that might have first infected cells with DNA. A good place to look, he says, would be a recently discovered group that infects amoebae, the mimiviruses[6]. These have huge, double-stranded DNA genomes — longer than those of some bacteria — and some of their genetic enzymes are similar to those in eukaryotes. Forterre also thinks that lab experiments with viruses and bacteria might recreate some aspects of the evolutionary process. It might be possible, for example, to replace a cell's DNA replication enzymes with their viral counterparts.

But can we ever really be sure about anything that happened so close to the origin of life? "It's an area of discourse rich in conjecture and poor in proofs, but I tend to be optimistic," says Eugene Koonin. A genomics researcher at the National Center for Biotechnology Information, based in Bethesda, Maryland, Koonin was the first proponent of the idea that DNA evolved twice. He says the idea of an RNA world shows that consensus — if not certainty — is possible, he says, and we can hope for the same regarding the origin of DNA. "The study of viral genomics is not going to come to fruition in the next five years, but it's not hopeless." ■

"Up to now there has been no convincing story of how DNA originated." — Patrick Forterre

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