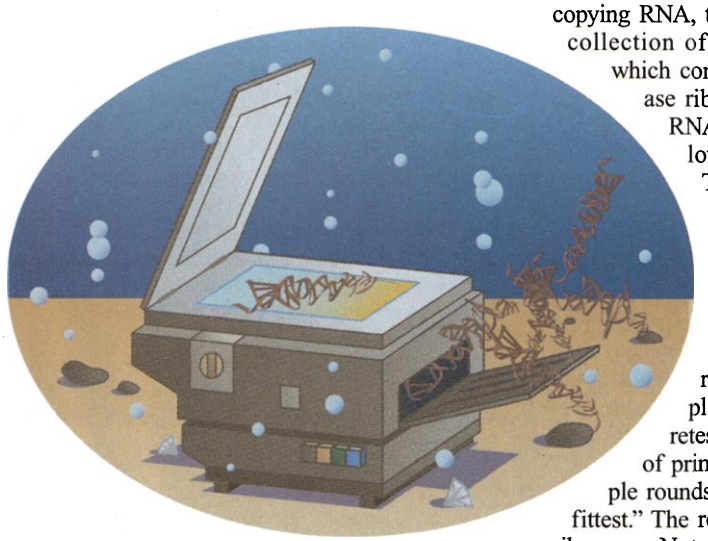
RIBOZYMES

Making Copies in the RNA World

By mimicking evolution in the lab, scientists have produced the first RNA enzyme that can make copies of other RNA molecules. The discovery provides a missing piece of evidence for a primitive biological world that existed before DNA and proteins entered the scene.

The discovery nearly 2 decades ago of ribozymes—RNA molecules that can catalyze chemical reactions—led to the idea



that modern life could have evolved from a primitive "RNA world." Doing the job of both DNA and proteins, RNA would carry genetic information and replicate that information to pass on to future generations. Subsequent discovery of additional ribozymes—including the heart of the protein-synthesizing ribosome (*Science*, 31 July 1998, p. 658, and 11 August 2000, p. 878)—has added to the credibility of the RNA world hypothesis. But scientists have been unable to show that molecules of RNA are actually capable of copying other RNA sequences, a job performed in the modern biochemical world by protein enzymes called RNA polymerases. That activity would be a critical component of an RNA world.

On page 1319 of this issue, Wendy Johnston and colleagues at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology (MIT) in Cambridge have now filled that key gap. They describe an enzyme, consisting of a stretch of RNA produced by in vitro evolution, that can make complementary copies of RNA molecules up to 14 nucleotides long, regardless of sequence, with impressive accuracy.

"The engine of the RNA world" would have to be able to do better than 14 nucleotides, says Gerald Joyce of the Scripps Research Institute in La Jolla, California, "but there's no doubt [now] that RNA [itself] is capable of doing polymerization."

David Bartel, leader of the Whitehead group, had previously selected from random RNA sequences an RNA molecule that could join two RNA strands end to end. He later discovered that this "RNA ligase" could also add a few nucleotides, the individual building blocks of RNA, onto the end of RNA molecules with specific sequences. Although not very robust, the ribozyme was performing the same chemical steps as "modern" protein enzymes that synthesize RNA.

To search for ribozymes that are better at copying RNA, the Whitehead team made a collection of RNA molecules, each of which consisted of Bartel's RNA ligase ribozyme linked to a 76-base RNA with random sequence followed by an RNA "primer." They screened 10^{15} of these randomized molecules for those that could add nucleotides to the end of the RNA primer, in a specific sequence dictated by an RNA template added to the reaction. The researchers amplified working molecules and retested them with different sets of primers and templates in multiple rounds of in vitro "survival of the fittest." The result was a vastly improved ribozyme. Not only could it make complementary copies of RNA templates 14 bases long, but most important, it could use any RNA sequence as a template, a generality that would be critical for a replicating ribozyme in an RNA world.

Bartel notes that the ribozyme stops adding bases not because it can't hold onto long pieces of RNA but because the best reaction conditions for polymerization are also optimal for chemical breakdown of RNA. That suggests that by tweaking the reaction conditions it should be possible to make RNA molecules longer than 14 nucleotides—a prerequisite for the RNA world. (The Whitehead team's ribozyme itself, for instance, is 189 nucleotides long.)

The ribozyme adds the right base onto RNA about 98.5% of the time. That pales in comparison to protein polymerases, which can achieve 99.99% accuracy. But, speculates Phillip Sharp of MIT, ribozymes in the RNA world may have only had to copy RNA sequences a few hundred bases long; longer units could have been spliced together by other ribozymes. That would make higher error rates tolerable.

The ribozyme's ability to generically recognize any RNA sequence is likely due to its interaction with chemical groups on an RNA molecule's backbone. The details of that interaction, however, await further structural studies. Those studies could reveal similarities with protein polymerases, says biochemist Tom Cech of the University of Colorado, Boulder, president of the Howard Hughes Medical Institute and co–Nobel Prize winner for the discovery of ribozymes. He notes that protein polymerases commonly resemble a hand, with catalysis occurring in the "palm" and a "thumb" and "finger" holding the substrate in place: "Maybe they started with a palm [the RNA ligase] and evolved a thumb and finger." –R. JOHN DAVENPORT

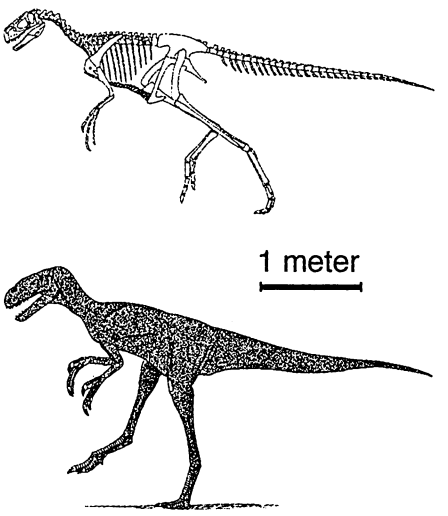
PALEONTOLOGY

Early Tyrannosaur Was Small But Well Armed

For all the fame of *Tyrannosaurus rex* and its relatives, their origins have been difficult to pin down. Now paleontologists have unveiled a skeleton of a primitive tyrannosauroid that backs up what many have suspected: The hulking predators evolved from smaller, long-armed creatures with grasping hands.

The classic view of *T. rex* ancestry held that it evolved from a long line of large meat eaters that stretched back about 80 million years to the Jurassic. An alternative idea, proposed in the 1920s, suggested that the tyrannosaurs of 65 million years ago descended from a group of more diminutive predators called the coelurosaurs, which is now known to include *Velociraptor*. The theory didn't catch on at the time, but it was revived in the 1990s and sometimes dubbed the "tyrannoraptor hypothesis." Yet despite the many anatomical similarities between tyrannosaurs and smaller coelurosaurs, no one had found a dinosaur that seemed transitional.

That gap is now filled by the 132-million-year-old *Eotyrannus*, found by an



Hands up. Unlike its later *T. rex* kin, *Eotyrannus* sported long, grasping forelimbs.

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