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RESEARCH NEWS

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Researchers Build Model Protocell Capable of Copying DNA

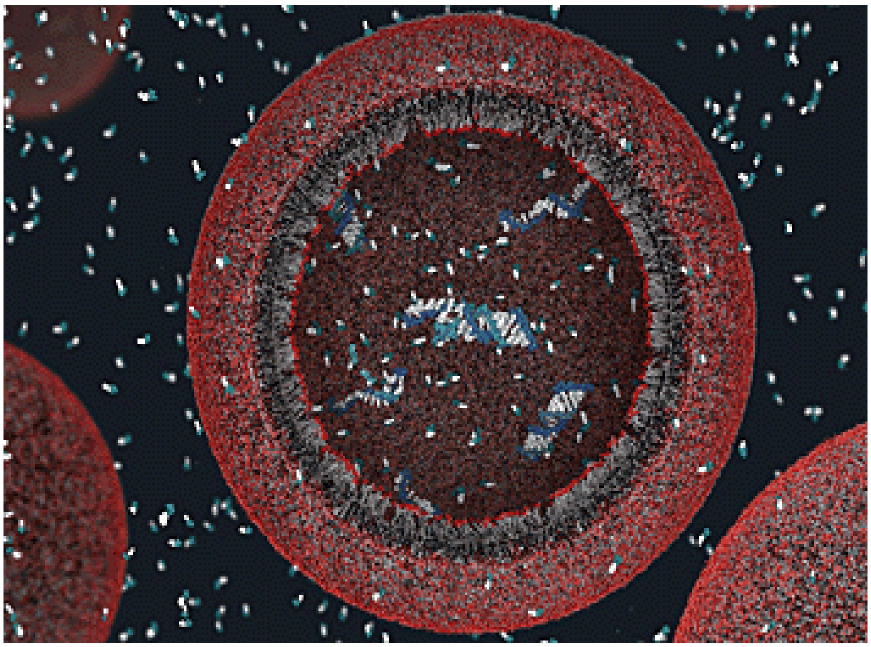

Image Title: The simple protocells that may have enabled life to develop four billion years ago consist of only genetic material surrounded by a fatty acid membrane. This pared down version of a cell—which has not yet been completely recreated in a laboratory—is thought to have been able to grow, replicate, and evolve. - Janet Iwasa

Four billion years ago, modern cells were absent on our still-young planet. The simple protocells that are thought to have given rise to Earth's earliest life forms were plentiful, but likely no more than a bit of genetic material surrounded by a hollow membrane.

Scientists have now created model protocells in the lab and demonstrated how they might have taken up the nutrients that propelled their growth. Howard Hughes Medical Institute (HHMI) investigator Jack Szostak and his research group fabricated DNA containing vesicles in the lab and showed that nutrients could enter the model protocell. Once inside, the nutrients assembled into a copy of the protocell's genetic material—an essential step in the origin of life.

Szostak, a molecular biologist at Massachusetts General Hospital, published his team's findings June 4, 2008, in an advance online publication in the journal *Nature.* The findings are the latest advance in Szostak's long-term effort to decipher how life arose on Earth. By building simple cell-like structures in a test tube, he and his colleagues are attempting to establish a plausible path that led primitive cells to emerge from simple chemicals. Ultimately, Szostak hopes to answer fundamental questions about evolution's earliest steps.

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>
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Cells are basically sacs encapsulated by bilayered membranes of lipids, plus proteins. A central question in evolution is how simple versions of these cells, or vesicles, first arose and began the competitive process that drove the evolution of life.

Membranes are essential components of even the simplest cells. They keep needed molecules readily accessible, and unneeded or harmful molecules safely outside. In modern cells, this barrier is rigorous: for most molecules to pass through, they must rely on the sophisticated pores, pumps, and channels that stud the membrane. Protocells, however, did not have the proteins needed to create these channels, and so scientists have long puzzled over how they could have acquired nutrients.

Szostak and his colleagues' work shows that simpler membranes, when composed of the right kind of lipids, allow essential molecules to enter a protocell without the help of proteins—and form genetic polymers once inside.

“What we're trying to do is to learn something about the origin of life by actually building an early cell,” says Szostak. Learning how the membrane works is a key part of that.

The membranes of modern cells are made of fatty molecules called phospholipids. The heads of the lipids are attracted to water, but the tails are not. So the lipids in the membrane arrange themselves into two layers that point in opposite directions—keeping the heads facing out toward the outside world and the watery interior of the cell, and the tails safely in the middle. Without channels, these membranes are impermeable to the nucleotides and other nutrients the cell needs.

“The cell 'wants'—so to speak—to have control over what gets in and what gets out,” Szostak says, explaining that in modern cells, channels open or close to admit the proper molecules in the proper amounts. “But if you're thinking about the origin of life, then obviously those complicated protein pumps and channels weren't around.”

According to Szostak, this means that early cell membranes would themselves have had to be permeable. “You still want something that's going to enclose the genetic material and keep it from floating away,” he says, “but you need something that's also going to allow the building blocks of the genetic material to get in.”

Szostak's lab had already created membrane sacs out of molecules called fatty acids—long chains of carbon atoms that make up part of the lipids in modern cell membranes. In the current study, they substituted different fatty acids with specific structural characteristics until they created a membrane with the appropriate permeability. They found that fatty acids that were branched, and therefore unable to pack tightly together, allowed sugar molecules (key building blocks of nucleotides, which in turn make up RNA and DNA) to pass through. Fatty acids with shorter carbon chains or bulky “headgroups” had a similar effect.

Guided by these findings, the group created a protocell out of fatty acids that were likely present in the earth's early environment. They were able to get nucleotides themselves to cross the membrane, showing that early cells could have taken up such molecules without protein channels.

Szostak says that's important, but only a part of the problem. Once inside the cell, the nucleotides need to be able to assemble into polymers that—like the DNA in modern cells—store genetic information. Modern cells replicate their DNA by “unzipping” the two strands of the molecule, and then using the individual strands as templates to create two daughter strands, again with the help of proteins. The second half of Szostak's experiment showed that his protocell could have carried out the template-copying part of the reaction.

The group created a protocell containing a single-stranded genetic molecule—a DNA template. Then, says Szostak, “we added nucleotides to the outside of the [protocell], let them diffuse across the membrane to the inside, and then take part in a template-copying reaction”—all without the help of proteins.

Despite the success of his model protocell in synthesizing a genetic polymer, Szostak says more work is needed. For one thing, he says, he hasn't yet been able to create the original strand of genetic material—only copy it. “This experiment is a model of that [particular] aspect of pre-biotic chemistry,” he says, but “we don't have the complete system yet.”

Once they can do that, Szostak wants to try creating a large number of protocells with different random genetic sequences inside. If he can do that, “we'd like to see the selection of some of those sequences that carry out useful functions.” Such an occurrence might represent how the first functional genes arose billions of years ago.

Szostak says there are still lots of other unanswered questions about the origins of life. He says his experiments represent just one idea, and it's not clear exactly what the original building blocks of life were. Beyond that, he says, “if you have all these building blocks, how do you get them to work together to exhibit biological behaviors like evolution? Then once you've got evolution going on, how does it gradually become more complex?”