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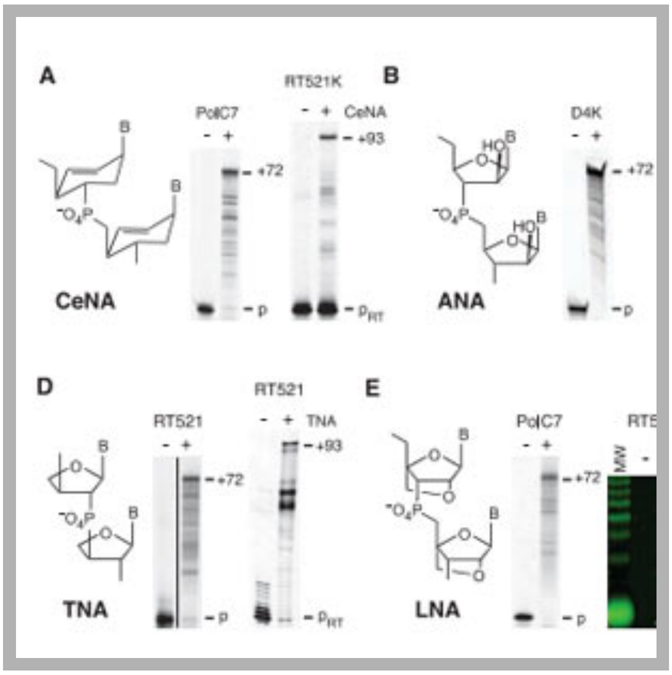
XNA: Synthetic DNA That Can Evolve

By swapping sugars in the DNA helix, scientists have created a new kind of genetic code that can function and evolve like regular DNA.

BY SARAH FECHT



Examples of XNA molecules.

Science / AAAS

Every living thing on Earth uses DNA or RNA to carry its genetic instructions for life. These two nucleic acids have different names because they're built from different sugars: DNA uses deoxyribose sugars for a backbone of its double helix, while RNA uses ribose. But what if other sugars could be used too?

Now scientists have shown that at least six other types of sugars can form nucleic acid backbones—and they can be used to store and retrieve genetic information. The researchers built DNA molecules from scratch, but replaced the deoxyribose with six other kinds of sugar, including hexitol, threose, and arabinose. The six types of synthetic genetic chains are called XNAs, or xeno-nucleic acids ("xeno" is Greek for "foreign"). And because XNA shows the possibility of heredity—passing down their genetic information—the researchers say these molecules not only could address fascinating questions about the origin of life, but also could open up the possibility of another kind of life based not on DNA and RNA.

Jack Szostak, a geneticist and Nobel laureate at Harvard University, tells PM in an email that the work "is very interesting with respect to the origin of life—in principle, many different polymers could serve the roles of RNA and DNA in living organisms. Why then does modern biology use only RNA and DNA?"

How to Make Synthetic DNA

This isn't the first time that geneticists have cooked up synthetic nucleic acids in a lab. Some scientists had previously created DNA with new kinds of base pairs beyond the A-T and C-G connections in DNA, and others had already created XNAs that incorporate foreign sugars. John Chaput, a molecular biologist at Arizona State University and an author on the new study in *Science*, says this work asks a new question: "How can you perform Darwinian evolution on something other than DNA or RNA? Lots of DNA and RNA molecules have been evolved in the laboratory, but going the next step and doing it on other molecules has been very challenging. This is one of the first examples of that."

To prove that XNAs could evolve, the researchers first had to create a new kind of enzyme to build the XNAs. Although it's possible to manufacture XNAs by machine, the resulting nucleic acids are short chains that have limited functionality and evolvability. So instead of using the machinated approach, the researchers took thousands of DNA-building enzymes and evolved them into XNA-building enzymes.

That required taking thousands of enzymes and mixing them together with XNA building blocks, as well as DNA strands that served as templates for the scaffolding on which to build XNA molecules. If an enzyme turned out to be good at building XNA strands, it was captured using a filtering process and amplified it for the next round of testing; enzymes that were bad at making XNA were washed away. Over many rounds of filtering, the enzyme population evolved to become more adroit at building XNAs—in fact, they could produce polymers XNA chains that lasted were five times longer than machine-made XNAs.

"They took enzymes that already existed, and evolved mutants of them that are better at making XNAs," says Floyd Romesberg, a chemist at the Scripps Research Institute, who called the technique "impressive."

Next, the researchers tried to evolve the XNAs themselves. To do so, they used a similar filtering technique. In this case, the scientists selected for XNAs that could bind to a specific protein; XNAs that did not bind to the proteins were washed away. Those that did bind were transcribed back into DNA so that they could be replicated. After replication, the team transcribed the copies back into XNA. In this way, the XNAs that had evolved to bind the protein were able to pass on that talent to a new generation of XNAs.

Synthetic DNA, Synthetic Life?

Because the XNAs are able to pass genetic information from one generation to the next and can adapt to the constraints of test tube evolution, Chaput says, XNAs could serve as the building blocks for completely new genetic systems. "Could you create synthetic life with it? That's possible, but it's much further down the road."

Szostak agrees, saying that "in the longer run, a very interesting implication is that it may be possible to design and build new forms of life that are based on one or more of these non-natural genetic polymers." But Romesberg emphasized that creating completely new life forms using XNA would be a long and difficult mission. The foremost challenge: Researchers must find an efficient way to reproduce XNAs directly into more XNAs without having to convert them to DNA and back again.

Some folks are nervous that releasing XNA into the biosphere could allow it to intermingle with DNA and RNA with unpredictable results. But scientists such as Steven Benner and Markus Schmidt retort that XNAs are foreign enough to be invisible to natural organisms (read more about this issue here).

Regardless of whether XNAs can or will be used to create new life forms, the researchers have shown that it is possible to expand evolution into systems based not on DNA or RNA. And the XNAs and their enzymes may also lead to some answers about why life as we know it is based on those to molecules only. Are DNA and RNA the best molecules to store genetic information and catalyze biological reactions, or did they become the building blocks of life by sheer happenstance? Now researchers will have the tools to test the true efficiency against lab-created competitors.

Medicine, too, could benefit from XNAs, Romesberg says. Doctors already prescribe biological products such as enzymes and antibodies to treat certain diseases, but these drugs break down quickly in the stomach and the blood stream. Because XNAs are somewhat foreign, they're not broken down as quickly in the body, as it has not evolved enzymes to digest them.

The experiment also has implications for looking for life on other planets. "Maybe if you look hard enough out in space, you might find a life form based on XNA," Chaput says.

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