Molecular alternatives to DNA, RNA offer new insight into life's origins

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Living systems owe their existence to a pair of information-carrying molecules: DNA and RNA. These fundamental chemical forms possess two features essential for life: they display heredity—meaning they can encode and pass on genetic information, and they can adapt over time, through processes of Darwinian evolution.

A long-debated question is whether heredity and evolution could be performed by molecules other than DNA and RNA.

John Chaput, a researcher at ASU's Biodesign Institute, who recently published an article in Nature Chemistry describing the evolution of threose nucleic acids, joined a multidisciplinary team of scientists from England, Belgium and Denmark to extend these properties to other so-called Xenonucleic acids or XNA's.

The group demonstrates for the first time that six of these unnatural nucleic acid polymers are capable of sharing information with DNA. One of these XNAs, a molecule referred to as anhydrohexitol nucleic acid or HNA was capable of undergoing directed evolution and folding into biologically useful forms.

Their results appear in the current issue of Science.

The work sheds new light on questions concerning the origins of life and provides a range of practical applications for molecular medicine that were not previously available.

Nucleic acid aptamers, which have been engineered through in vitro selection to bind with various molecules, act in a manner similar to antibodies—latching onto their targets with high affinity and specificity. "This could be great for building new types of diagnostics and new types of biosensors," Chaput says, pointing out that XNAs are heartier molecules, not recognized by the natural enzymes that tend to degrade DNA and RNA. New therapeutics may also arise from experimental Xenobiology.

Both RNA and DNA embed data in their sequences of four nucleotides—information vital for conferring hereditary traits and for supplying the coded recipe essential for building proteins from the 20 naturally occurring amino acids. Exactly how (and when) this system got its start however, remains one of the most intriguing and hotly contested areas of biology.

According to one hypothesis, the simpler RNA molecule preceded DNA as the original informational conduit. The RNA world hypothesis proposes that the earliest examples of life were based on RNA and simple proteins. Because of RNA's great versatility—it is not only capable of carrying genetic information but also of catalyzing chemical reactions like an enzyme—it is believed by many to have supported pre-cellular life.

Nevertheless, the spontaneous arrival of RNA through a sequence of purely random mixing events of primitive chemicals was at the very least, an unlikely occurrence. "This is a big question," Chaput says. "If the RNA world existed, how did it come into existence? Was it spontaneously produced, or was it the product of something that was even simpler than RNA?"

This pre-RNA world hypothesis has been gaining ground, largely through investigations into XNAs, which provide plausible alternatives

to the current biological regime and could have acted as chemical stepping-stones to the eventual emergence of life. The current research strengthens the case that something like this may have taken place.

Threose nucleic acid or TNA for example, is one candidate for this critical intermediary role. "TNA does some interesting things," Chaput says, noting the molecule's capacity to bind with RNA through antiparallel Watson-Crick base pairing. "This property provides a model for how XNAs could have transferred information from the pre-RNA world to the RNA world."

Nucleic acid molecules, including DNA and RNA consist of 3 chemical components: a sugar group, a triphosphate backbone and combinations of the four nucleic acids. By tinkering with these structural elements, researchers can engineer XNA molecules with unique properties. However, in order for any of these exotic molecules to have acted as a precursor to RNA in the pre-biotic epoch, they would need to have been able to transfer and recover their information from RNA. To do this, specialized enzymes, known as polymerases are required.

Nature has made DNA and RNA polymerases, capable of reading, transcribing and reverse transcribing normal nucleic acid sequences. For XNA molecules, however; no naturally occurring polymerases exist. So the group, led by Phil Holliger at the MRC in England, painstakingly evolved synthetic polymerases that could copy DNA into XNA and other polymerases that could copy XNA back into DNA. In the end, polymerases were discovered that transcribe and reverse-transcribe six different genetic systems: HNA, CeNA, LNA, ANA, FANA and TNA. The experiments demonstrated that these unnatural DNA sequences could be rendered into various XNAs when the polymerases were fed the appropriate XNA substrates.

Using these enzymes as tools for molecular evolution, the team evolved

the first example of an HNA aptamer through iterative rounds of selection and amplification. Starting from a large pool of DNA sequences, a synthetic polymerase was used to copy the DNA library into HNA. The pool of HNA molecules was then incubated with an arbitrary target. The small fraction of molecules that bound the target were separated from the unbound pool, reverse transcribed back into DNA with a second synthetic enzyme and amplified by PCR. After many repeated rounds, HNAs were generated that bound HIV trans-activating response RNA (TAR) and hen egg lysosome (HEL), which were used as binding targets.) "This is a synthetic Darwinian process," Chaput says. "The same thing happens inside our cells, but this is done in vitro."

The method for producing XNA polymerases draws on the path-breaking work of Holliger, one of the lead authors of the current study. The elegant technique uses cell-like synthetic compartments of water/oil emulsion to conduct directed evolution of enzymes, particularly polymerases. By isolating self-replication reactions from each other, the process greatly improves the accuracy and efficiency of polymerase evolution and replication. "What nobody had really done before," Chaput says, "is to take those technologies and apply them to unnatural nucleic acids. "

Chaput also underlines the importance of an international collaboration for carrying out this type of research, particularly for the laborious effort of assembling the triphosphate substrates needed for each of the 6 XNA systems used in the study:

"What happened here is that a community of scientists came together and organized around this idea that we could find polymerases that could be used to open up biology to unnatural polymers. It would have been a tour de force for any lab to try to synthesize all the triphosphates, as none of these reagents are commercially available."

The study advances the case for a pre-RNA world, while revealing a new class of XNA aptamers capable of fulfilling myriad useful roles. Although many questions surrounding the origins of life persist, Chaput is optimistic that solutions are coming into view: "Further down the road, through research like this, I think we'll have enough information to begin to put the pieces of the puzzle together."

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