Simpler times: Did an earlier genetic molecule predate DNA and RNA?

January 9 2012, by Richard Harth

The nucleic acid TNA may have acted as a precursor molecule to DNA and RNA, bearing genetic information and performing important biological functions. Photo: Public domain

(PhysOrg.com) -- In the chemistry of the living world, a pair of nucleic acids—DNA and RNA—reign supreme. As carrier molecules of the genetic code, they provide all organisms with a mechanism for faithfully reproducing themselves as well as generating the myriad proteins vital to living systems.

Yet according to John Chaput, a researcher at the Center for Evolutionary Medicine and Informatics, at Arizona State University's Biodesign Institute®, it may not always have been so.

Chaput and other researchers studying the first tentative flickering of life on earth have investigated various alternatives to familiar genetic molecules. These chemical candidates are attractive to those seeking to unlock the still-elusive secret of how the first life began, as primitive molecular forms may have more readily emerged during the planet's prebiotic era.

One approach to identifying molecules that may have acted as genetic precursors to RNA and DNA is to examine other nucleic acids that differ slightly in their chemical composition, yet still possess critical properties of self-assembly and replication as well as the ability to fold into shapes useful for biological function.

According to Chaput, one interesting contender for the role of early genetic carrier is a molecule known as TNA, whose arrival on the primordial scene may have predated its more familiar kin. A nucleic acid similar in form to both DNA and RNA, TNA differs in the sugar component of its structure, using threose rather than deoxyribose (as in DNA) or ribose (as in RNA) to compose its backbone.

In an article released online today in the journal *Nature Chemistry*, Chaput and his group describe the Darwinian evolution of functional TNA molecules from a large pool of random sequences. This is the first case where such methods have been applied to molecules other than DNA and RNA, or very close structural analogues thereof. Chaput says "the most important finding to come from this work is that TNA can fold into complex shapes that can bind to a desired target with high affinity and specificity". This feature suggests that in the future it may be possible to evolve TNA enzymes with functions required to sustain early life forms.

Nearly every organism on earth uses DNA to encode chunks of genetic information in genes, which are then copied into RNA. With the aid of

specialized enzymes known as polymerases, RNA assembles amino acids to form essential proteins. Remarkably, the basic functioning of the genetic code remains the same, whether the organism is a snail or a senator, pointing to a common ancestor in the DNA-based microbial life already flourishing some 3.5 billion years ago.

Nevertheless, such ancestors were by this time quite complex, leading some scientists to speculate about still earlier forms of self-replication. Before DNA emerged to play its dominant role as the design blueprint for life, a simpler genetic world dominated by RNA may have prevailed. The RNA world hypothesis as it's known alleges that ribonucleic acid (RNA) acted to store genetic information and catalyze chemical reactions much like a protein enzyme, in an epoch before DNA, RNA and proteins formed the integrated system prevalent today throughout the living world.

While the iconic double helix of DNA is formed from two complimentary strands of nucleotides, attached to each other by base pairing in a helical staircase, RNA is single-stranded. The two nucleic acids DNA and RNA are named for the type of sugar complex that forms each molecule's sugar-phosphate backbone—a kind of molecular thread holding the nucleotide beads together.

Could a simpler, self-replicating molecule have existed as a precursor to RNA, perhaps providing genetic material for earth's earliest organisms? Chaput's experiments with the nucleic acid TNA provide an attractive case. To begin with, TNA uses tetrose sugars, named for the four-carbon ring portion of their structure. They are simpler than the five-carbon pentose sugars found in both DNA and RNA and could assemble more easily in a prebiotic world, from two identical two-carbon fragments.

This advantage in structural simplicity was originally thought to be an Achilles' heel for TNA, making its binding behavior incompatible with

DNA and RNA. Surprisingly, however, research has now shown that a single strand of TNA can indeed bind with both DNA and RNA by Watson-Crick base pairing—a fact of critical importance if TNA truly existed as a transitional molecule capable of sharing information with more familiar nucleic acids that would eventually come to dominate life.

In the current study, Chaput and his group use an approach known as molecular evolution to explore TNA's potential as a genetic biomolecule. Such work draws on the startling realization that fundamental Darwinian properties—self-replication, mutation and selection—can operate on non-living chemicals.

Extending this technique to TNA requires polymerase enzymes that are capable of translating a library of random DNA sequences into TNA. Once such a pool of TNA strands has been generated, a process of selection must successfully identify members that can perform a given function, excluding the rest. As a test case, the team hoped to produce through molecular evolution, a TNA strand capable of acting as a high-specificity, high-affinity binding receptor for the human protein thrombin.

They first attempted to demonstrate that TNA nucleotides could attach by complementary base pairing to a random sequence of DNA, forming a hybrid DNA-TNA strand. A DNA polymerase enzyme assisted the process. Many of the random sequences, however, contained repeated sections of the guanine nucleotide, which had the effect of pausing the transcription of DNA into TNA. Once random DNA libraries were built excluding guanine, a high yield of DNA-TNA hybrid strands was produced.

The sequences obtained were 70 nucleotides in length, long enough Chaput says, to permit them to fold into shapes with defined binding sites. The DNA-TNA hybrids were then incubated with the target

molecule thrombin. Sequences that bound with the target were recovered and amplified through PCR. The DNA portion was removed and used as a template for further amplification, while the TNA molecules displaying high-affinity, high specificity binding properties were retained.

Additionally, the binding affinity of the evolved and selected TNA molecules was tested against two other common proteins, for which they displayed no affinity, strengthening the case that a highly specific binding molecule had resulted from the group's directed evolution procedure.

Chaput suggests that issues concerning the prebiotic synthesis of ribose sugars and the non-enzymatic replication of RNA may provide circumstantial evidence of an earlier genetic system more readily produced under primitive earth conditions. Although solid proof that TNA acted as an RNA precursor in the prebiotic world may be tricky to obtain, Chaput points to the allure of this molecule as a strong candidate, capable of storing information, undergoing selection processes and folding into tertiary structures that can perform complex functions. This result provides the motivation to explore TNA as an early genetic system.

Chaput is optimistic that major questions about the prebiotic synthesis of TNA, its role in the origin and early evolution of life on earth, and eventual genetic takeover by RNA will, over time, be answered.

More information: "Darwinian evolution of an alternative genetic system provides support for TNA as an RNA progenitor", DOI: 10.1038/nchem.1241