DNA size a crucial factor in genetic mutations, study finds

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Researchers at Stanford University have created a larger-than-normal DNA molecule that is copied almost as efficiently as natural DNA. The findings, reported in the Oct. 25 online edition of the *Proceedings of the National Academy of Sciences* (PNAS), may reveal new insights into how genetic mutations-tiny mistakes that occur during DNA replication-arise. The discovery was made in the laboratory of Eric Kool, a professor of chemistry at Stanford and co-author of the PNAS study.

DNA, the genetic encoder of life, comes in two parallel strands that form a double helix. It's like a long, twisted ladder where each rung consists of two molecules that form a base pair. DNA has four bases: adenosine (A), thymine (T), guanine (G) and cytosine (C). A always pairs with T, and G with C. To copy itself, the DNA molecule unwinds and splits. Either strand is now a template to build a new DNA molecule. An enzyme-a protein that speeds the reaction, in this case the bacteria E. coli's DNA polymerase I-moves along the template and selects the corresponding base to create a new base pair.

DNA bases fit into a specialized site on the enzyme before they are bonded to the template. Kool wanted to see how the enzyme reacts if the bases are not the usual size. "The idea was to see how DNA replication depends on size," Kool says.

The researchers investigated it by offering bases of different sizes to the DNA polymerase I enzyme and measuring how accurately the enzyme made new DNA copies. About once every 10,000 to 100,000 times the enzyme will put in the wrong base, choosing for instance a G instead of a T to pair with an A. The rate that the enzyme accurately copies DNA is known as its efficiency.

These rare and random mistakes can cause genetic mutations. While we tend to heap negative connotations onto the term, some mutations create new traits that actually benefit the organism or yield no effect. These small-scale changes, collectively called genetic drift, play an important role in evolution, as does natural selection.

To make their DNA bases, Kool started with a molecule similar to thymine-called an analog-and made five different sizes by adding increasingly larger atoms. The first analog was smaller than natural thymine, the second about the same size and the last three were increasingly larger. The difference between the smallest and largest analogs was only one angstrom, or a tenth of a nanometer.

Bigger is better

When the researchers offered the analog bases to DNA polymerase I, the enzyme not only recognized the synthetic molecules as it would natural DNA but also copied one of the slightly larger analogs at a rate 22 times more efficiently than the natural-sized analog. In fact, DNA polymerase I incorporated the slightly larger analog almost as efficiently as it did natural thymine, both in the test tube and in live E. coli bacteria. In contrast to this, the smallest and largest analogs in the set were rejected by the enzyme and the bacteria.

According to Kool, these results indicate that size is a strong factor determining enzyme efficiency-and a mechanism for allowing mutations into the DNA molecule.

"It's a way the organism can evolve," Kool says. "If the protein that copies DNA prefers a molecule that's slightly bigger than natural DNA, then it can accept mistakes more readily." For example, although T is supposed to match up with A, it might be inclined to pair with G, which has a slightly larger configuration.

The sheer fact that a living system readily used a base-or nucleotide-that was artificially created is itself groundbreaking. "Here we have, I think, the first example of an efficient, human-designed nucleotide working in a live cell," he says.

Kool and the gang are now exploring "the funny finding that the bugs prefer DNA that's larger than natural DNA" by making larger nucleotides. "Size and shape are related issues, so we're interested now in keeping the size constant and changing the shape," Kool adds.

Source: Stanford University

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