Redefining DNA: Darwin from the atom up

March 23 2009

In a dramatic rewrite of the recipe for life, scientists from Florida today described the design of a new type of DNA with 12 chemical letters instead of the usual four. Presented here at the 237th National Meeting of the American Chemical Society (ACS), this artificial genetic system already is helping to usher in the era of personalized medicine for millions of patients with HIV, hepatitis and other diseases.

The research may also shed light on how life arose on Earth, by producing a self-sustaining molecule capable of Darwinian evolution and reproduction, much like one that many scientists suggest arose at the dawn of life on Earth nearly four billion years ago.

Led by Steven Benner, Ph.D., this team is rewriting the rulebook that Nobel laureates James Watson and Francis Crick started when they described DNA's structure in 1953. One of the crowning discoveries of 20th century science, Watson and Crick's discovery established how the four chemical "letters" of DNA — A, T, C and G — pair up.

"This is a man on the moon goal," says Steven Benner, Ph.D. "It has dragged us kicking and screaming into uncharted territory. But we've learned all sorts of reasons about how the Watson and Crick rules don't enable technology to do useful things like highly parallel amplification of DNA or highly parallel diagnosis of human diseases. These things are worth a lot of money."

These pairing rules, for instance, make it very difficult for researchers to develop multiplexed diagnostic tests for viral diseases — tests that

require identification and tagging of viral DNA. Old methods used regular DNA to bind and tag foreign genetic material. But natural DNA would often bind with non-disease DNA and generate confusing false positive and false negative results.

Benner's artificial genetic system does not operate under Watson-Crick rules, so the tagging gives accurate results. Benner's artificial alphabet already has been applied commercially. It is the basis of a viral load detector, which helps personalize the health care of those 400,000 patients annually infected with hepatitis B, hepatitis C, and HIV, the cause of AIDS.

"This is a hundred million dollar product right now," Benner noted. "It's used to manage cystic fibrosis, as well. We can also use this technology to go into biological samples and extract known genes with cancer-causing mutations. We can do all of this because we have an artificial DNA system.

For patients with HIV and hepatitis, the viral load detector can mean the difference between life and death.

Modern drug cocktails for these diseases are highly effective, reducing the viral load in the bloodstream to nearly zero. But at some point, the virus mutates, enabling it to evade the drugs and repopulate. As the viral tide rises, there are no outward symptoms in the patient, so the mutated strain is often discovered long after the virus has spread again.

The viral load detector, which relies on Benner's 12 letter system to tag DNA, may change that.

"What we want to do with personalized care is to give you a cocktail, and then monitor you and discover when the virus becomes resistant to it," explains Benner. "Now we don't want to do that too soon - that would

waste a lifetime of good viral inhibitors — but not too late, of course. The patient would go in once a month to get their viral load measured. At some point the virus mutates and its viral load goes up. Then you know you better change the cocktail."

Benner says that the artificial DNA system is poised to become an essential tool in genomics research. The 12 letter alphabet already underlies new work at the National Human Genome Research Institute to connect large quantities of genomic data with human medicine.

The 12 letter system might also shed light on one of most mysterious times in Earth's history — the dawn of life nearly four billion years ago. Many scientists believe that this might have occurred when DNA's ancient cousin, RNA, began to act like a living organism.

"The idea has been that life originated on earth as RNA molecules assembled randomly and spontaneously in the prebiotic soup," says Benner. "Then, one of them found the ability to make copies of itself. In doing so, it made those copies with imperfections, so that some of its 'kids' were a bit better. Most were worse, so the better ones took over more resources. That started Darwinian processes. The rest is history."

Benner's ultimate goal is to synthesize a similar life form in his lab at the Foundation for Applied Molecular Evolution. His 12 letter genetic system is capable of nearly all of the actions that define a living thing — reproduction, growth and response to its environment — all without the benefit of genes refined over billions of years of evolution.

"But it still isn't self-sustaining," Benner explains. "You need a graduate or post-doc to come in the morning and feed it. It doesn't look for its own food. No one has gotten that first step to work. If you start making estimates of how many molecules you have to look for in order to find one that does this, you're talking about

10,000,000,000,000,000,000,000,000,000,000,000 molecules."

While Benner continues to pursue a chemical system fully capable of Darwinian evolution, he emphasized the lessons already learned from the development of the 12 letter system.

"We haven't just taken things from nature, but we've actually understood something about how chemical structure is related to genetic behavior. With that, we've been able to make new versions of it," says Benner.

Source: American Chemical Society (news : web)