MedicalXpress

Study of huge numbers of genetic mutations point to oxidative stress as underlying cause

September 7 2009

A study that tracked genetic mutations through the human equivalent of about 5,000 years has demonstrated for the first time that oxidative DNA damage is a primary cause of the process of mutation - the fuel for evolution but also a leading cause of aging, cancer and other diseases.

The research, just published in Proceedings of the National Academy of Sciences, also indicated that natural selection is affecting the parts of the genome that don't contain genes - supposedly "junk" DNA that increasingly appears to have important roles in life processes that are very poorly understood.

The analysis was done by scientists at Oregon State University, Indiana University, the University of Florida and University of New Hampshire, in studies supported by the National Institutes of Health.

This research was unusual, scientists say, because the model animal used for the study, a type of roundworm called *C. elegans*, was tracked through 250 generations and in that period of time accumulated 391 genetic mutations through normal life processes. That's more than 10 times as many mutations as have ever before been tracked in a study such as this.

Several Nobel Prizes have been awarded based on studies done with this roundworm, which was the first animal to have its entire genome sequenced. And despite their vast evolutionary separation as life forms, this tiny roundworm and humans still share comparable forms of DNA

maintenance.

"Genetic mutations in animals are actually pretty rare, they don't happen very often unless they are induced by something," said Dee Denver, an assistant professor of zoology at OSU and principal investigator on the study. "The value of using this roundworm is that it reaches reproductive age in about four days, so we can study changes that happen through hundreds of generations, using advanced genome sequencing technology."

Genetic mutations can take various forms, such as a disruption in the sequence of DNA bases, larger deletions of whole sections of DNA, or other events. They are a fundamental part of the biological process of life and the basis of evolution, allowing organisms to change - sometimes in ways that are good and lead to greater survival value, sometimes bad and leading to decline or death. But the process is difficult to study and a real understanding of the driving forces behind mutation, its frequency, and the types of mutation that happen most often has been elusive, researchers say.

A primary finding of the new study is that a predominant number of genetic mutations - most, but not all of them - are linked to guanine, one of the four basic nucleotides that make up DNA and form the genetic code of life. Guanine is known to be particularly sensitive to oxidative damage.

"Most life on Earth depends in some form on oxygen, which is great at the production of energy," Denver said. "But we pay a high price for our dependence on oxygen, because the process of using it is not 100 percent efficient, and it can result in free oxygen radicals that can damage proteins, fats and DNA. And this process gets worse with age, as free radicals accumulate and begin to cause disease."

This is one of the first studies, Denver said, that is clearly demonstrating the effects of oxidative damage at a genome-wide scale.

"The research showed that the majority of all DNA mutations bear the signature of oxidative stress," Denver said. "That's exactly what you would expect if you believe that oxidative stress is an underlying cause of aging and disease."

Beyond that, however, the study also found that mutation and natural selection is also operating in the "junk DNA" parts of the roundworm, which actually comprises about 75 percent of its genome but traditionally was not thought to play any major role in life and genetic processes. This suggests that these poorly-understood and little appreciated parts of the genome may have important biological roles that are not yet known, Denver said.

Oxidative stress for decades has been suspected as a mechanism for some of the processes that lead to aging and disease, and it has been studied extensively for that reason. This research provides a better fundamental understanding of the genetic impacts of oxidative stress and its role in both genetic disease and evolution, researchers say.

Source: Oregon State University (news : web)