Ancient retroviruses spurred evolution of gene regulatory networks in humans and other primates

14 November 2007

When ancient retroviruses slipped bits of their DNA into the primate genome millions of years ago, they successfully preserved their own genetic legacy. Today an estimated 8 percent of the human genetic code consists of endogenous retroviruses (ERVs)--the DNA remnants from these so-called "selfish parasites."

Surprisingly, the infected hosts and their primate descendants also appear to have benefited from this genetic invasion, new evidence suggests. The ancient retroviruses--distant relatives of the human immunodeficiency virus (HIV)--helped a gene called p53 become an important "master gene regulator" in primates, according to a study published this week in the online early edition of *Proceedings of the National Academy of Sciences*.

The study, led by researchers at the University of California, Santa Cruz, offers an explanation for how regulatory networks of genes evolved. Not all genes are created equal; some are masters that can selectively turn on and off many other genes. The advent of gene regulatory networks allowed for greater control over gene expression in higher vertebrates. With tightly controlled variations in gene expression, species that had very similar genetic codes--for instance, humans and chimpanzees--could nevertheless exhibit striking differences.

Scientists have long wondered how a master regulator such as p53 gained the ability to turn on and off a broad range of other genes related to cell division, DNA repair, and programmed cell death. How did p53 build its complex and powerful empire, so to speak"

Using the tools of computational genomics, the UCSC team gathered compelling evidence that retroviruses helped out. ERVs jumped into new positions throughout the human genome and spread numerous copies of repetitive DNA sequences that allowed p53 to regulate many other genes, the team contends.

"This would have provided a mechanism to quickly establish a gene regulatory network in a very short evolutionary time frame," said Ting Wang, a post-doctoral researcher at UCSC and lead author of the paper.

Thus, p53 was crowned "guardian of the genome," as biologists now call it. Its job is to coordinate the surveillance system that monitors the well-being of cells. Indeed, p53 is so important that when it fails, cancer often results. About half of all human tumors contain a mutated or defective p53 gene.

"Our work provides a new window on the complex biology of p53," said coauthor David Haussler, a professor of biomolecular engineering at UCSC and a Howard Hughes Medical Institute Investigator. "From a biomedical standpoint, it's important because these changes only occurred in the primate lineage, not in mice."

By analyzing and comparing genetic data from different species, the team estimated that certain ERVs entered the genome about 40 million years ago, and spread rapidly in primates about 25 million years ago.

Scientists have long suspected that retroviral elements could play a role in gene regulation. More than 50 years ago, Nobel Laureate Barbara McClintock observed that transposable elements--or "jumping genes"--altered gene expression in maize. In 1971, Roy Britten and Eric Davidson theorized that commonly observed repetitive DNA sequences actually served as codes for gene regulatory networks. The DNA remnants of

retroviruses tend to be repetitive sequences and can jump around, when active.

The UCSC team finally gathered concrete evidence to support Britten and Davidson's hypothesis. The group trolled the human genome for ERVs, identified p53 binding sites in them, and tested their ability to activate genes regulated by p53. More than one-third of all known p53-binding sites turned out to be associated with ERVs, they discovered.

These results raise new questions about the role of so-called "junk DNA," the vast regions of the genome that don't code for proteins. ERVs fall into that category. Many scientists once believed that such DNA served no purpose, but new data from the Haussler lab and other labs are challenging that view.

"We're starting to uncover the treasure in this junk," said Wang.

Moreover, the team has proposed a new mechanism for evolutionary change. Conventional wisdom says that evolution is driven by small changes--point mutations--to the genetic code. If a change is beneficial, the mutation is passed onto future generations.

Now it appears that another level of evolution occurs that is not driven by point mutations. Instead, retroviruses insert DNA sequences and rearrange the genome, which leads to changes in gene regulation and expression. If such a change in gene regulation is beneficial, it is passed onto future generations.

This research should have broad implications, according to Wang.

"Our prediction is that this is a general mechanism that has been around ever since viruses," Wang said. "ERV-mediated expansion of a gene regulatory network probably happened more than once and not just in primates. We predict it led to other master gene regulators, not just p53."

Source: University of California - Santa Cruz

APA citation: Ancient retroviruses spurred evolution of gene regulatory networks in humans and other primates (2007, November 14) retrieved 21 October 2019 from https://phys.org/news/2007-11-ancient-retroviruses-spurred-evolution-gene.html

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