Head-on collisions between DNA-code reading machineries accelerate gene evolution

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Houra Merrikh, assistant professor of microbiology, and her student Samuel Million-Weaver, University of Washington, study mechanisms that bacteria use to evolve and adapt. Credit: Christopher Merrikh

Bacteria appear to speed up their evolution by positioning specific genes along the route of expected traffic jams in DNA encoding. Certain genes

are in prime collision paths for the moving molecular machineries that read the DNA code, as University of Washington scientists explain in this week's edition of *Nature*.

The spatial-organization tactics their model organism, *Bacillus subtilis*, takes to evolve and adapt might be imitated in other related Gram-positive bacteria, including harmful, ever-changing germs like staph, strep, and listeria, to strengthen their virulence or cause persistent infections. The researchers think that these mechanisms for accelerating evolution may be found in other living creatures as well.

Replication – the duplicating of the genetic code to create a new set of genes– and transcription – the copying of DNA code to produce a protein – are not separated by time or space in bacteria. Therefore, clashes between these machineries are inevitable. Replication traveling rapidly along a DNA strand can be stalled by a head-on encounter or same-direction brush with slower-moving transcription.

The senior authors of the study, Houra Merrikh, UW assistant professor of microbiology, and Evgeni Sokurenko, UW professor of microbiology, and their research teams are collaborating to understand the evolutionary consequences of these conflicts. The major focus of Merrikh and her research team is on understanding mechanistic and physiological aspects of conflicts in living cells – including why and how these collisions lead to mutations.

Impediments to replication, they noted, can cause instability within the genome, such as chromosome deletions or rearrangements, or incomplete separation of genetic material during cell division. When dangerous collisions take place, bacteria sometimes employ methods to repair, and then restart, the paused DNA replication, Merrikh discovered in her earlier work at the Massachusetts Institute of Technology.

To avoid unwanted encounters, bacteria orient most of their genes along what is called the leading strand of DNA, rather than the lagging. The terms refer to the direction the encoding activities travel on different forks of the unwinding DNA. Head-on collisions between replication and transcription happen on the lagging strand.

Despite the heightened risk of gene-altering clashes, the study bacteria *B. subtilis* still orients 25 percent of all its genes, and 6 percent of its essential genes, on the lagging strand.

The scientist observed that genes under the greatest natural selection pressure for amino-acid mutations, a sign of their adaptive significance, were on the lagging strand. Amino acids are the building blocks for proteins. Based on their analysis of mutations on the leading and the lagging strands, the researchers found that the rate of accumulation of mutations was faster in the genes oriented to be subject to head-on replication-transcription conflicts, in contrast to co-directional conflicts.

According to the researchers, together the mutational analyses of the genomes and the experimental findings indicate that head-on conflicts were more likely than same-direction conflicts to cause mutations. They also found that longer genes provided more opportunities for replication-transcription conflicts to occur. Lengthy genes were more prone to mutate.

The researchers noted that head-on replication-transcription encounters, and the subsequent mutations, could significantly increase structural variations in the proteins coded by the affected genes. Some of these chance variations might give the bacteria new options for adapting to changes or stresses in their environment. Like savvy investors, the bacteria appear to protect most of their genetic assets, but offer a few up to the high-roll stakes of mutation.

The researchers pointed out, "A simple switch in gene orientation …could facilitate evolution in specific genes in a targeted way. Investigating the main targets of conflict-mediated formation of mutations is likely to show far-reaching insights into adaptation and evolution of organisms."

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