R-loops break walls of gene silencing

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(Medical Xpress) -- Researchers at the University of California, Davis, have figured out how the human body keeps essential genes switched "on" and silences the vast stretches of genetic repeats and "junk" DNA.

Frédéric Chédin, associate professor in the Department of Molecular and Cellular Biology, describes the research in a paper published today (March 1) in the journal *Molecular Cell*. The work could lead to treatments for lupus and other autoimmune diseases, by reversing the gene-silencing process known as cytosine methylation.

"R-loops" are the key, say graduate student Paul Ginno, Chédin and colleagues. The loops emerge in the RNA transcription process in DNA sections that are rich in cytosine and guanine, the C and G in the four-letter DNA code. These C and G stretches serve as "on" switches, or promoters, for about 60 percent of human genes.

Scientists have known since the 1980s that these so-called CG island promoters are not subject to methylation. But, Chédin said, the mechanism has been a long-standing mystery.

The UC Davis researchers built a catalog of almost 8,000 CG islands in the human genome, studied their DNA sequences and found the CG sequences to be skewed toward having one strand of the double helix rich in guanine, and the complementary strand rich in cytosine.

Then, in RNA transcription, the G-rich RNA remains stably bound to a C-rich DNA strand, forcing the G-rich DNA strand into a loop — which

then prevents methylation.

DNA methylation is considered part of the new field of epigenetics, which studies inheritable genetic changes that are not directly coded in the DNA sequence. However, the new work shows that, at least at CG islands, the epigenetic state is determined by the DNA sequence.

Scientists know that reduced methylation of DNA plays a key role in triggering autoimmunity in lupus, Chédin said. However, the molecular events behind this DNA under-methylation have been unclear.

“Our work establishes that excessive R-loop formation may drive under-methylation and autoimmunity,” Chédin said.

Co-authors: Paul Lott, graduate student; Holly Christensen, undergraduate; and Ian Korf, associate professor in the Department of Molecular and Cellular Biology and the Genome Center.

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