

NIEHS scientists identify a novel signal for mismatch repair

By Heather Franco

Errors are incorporated into DNA as it is copied by DNA polymerase enzymes, in a process known as DNA replication. Correcting these errors is imperative to prevent detrimental mutations, which can lead to diseases, such as cancer. However, to maintain the genomic stability essential to human health, the repair machinery needs to be directed to the newly copied strand, so as to not introduce mutations into the template DNA.

In a new [study](http://www.ncbi.nlm.nih.gov/pubmed/23603118) (<http://www.ncbi.nlm.nih.gov/pubmed/23603118>) published May 9 in *Molecular Cell*, Scott Lujan, Ph.D., and colleagues in the NIEHS DNA Replication Fidelity Group, headed by lead researcher Thomas Kunkel, Ph.D., uncovered an identification signal on the newly copied DNA strand that marks it for repair. They demonstrated, for the first time, the role of a key enzyme, RNase H2, in directing the mismatch repair machinery to the correct strand. This work may lead to a new understanding of the development of some cancers and neurodevelopmental disorders.

Understanding mechanisms of mismatch repair

Lujan explained that maintaining genomic integrity is essential for the survival of an organism, and it is achieved through DNA replication and its accompanying repair processes. Each strand of the double helical template DNA is copied in a unique manner, with the leading strand synthesized processively and the lagging strand synthesized in small segments known as Okazaki fragments.

According to Lujan, several specialized enzymes, called polymerases, have evolved to copy the different strands. Interestingly, the leading strand polymerase has a highly conserved sequence that, when introduced into lagging strand polymerases, makes them more prone to insert both ribonucleotides and incorrect DNA bases. The reverse is true when the equivalent sequence from lagging strand polymerases is introduced into the leading strand polymerase.

“It appears that the leading strand polymerase has evolved to prevent more frequent misinsertion of DNA bases, due to this sequence, while maintaining an elevated ribonucleotide insertion rate,” Lujan said. “This implies that leading strand ribonucleotides serve some positive function that outweighs their risk, as their presence leads to genomic instability.”

One mechanism by which errors in the DNA sequence are corrected is mismatch repair, in the study of which Kunkel has been a leading authority for almost 20 years. As Kunkel explained, “Mismatch repair of replication errors is like the spell-check function on a word processor, and is critical for correctly duplicating genetic information.” As part of the repair process, he said, the ribonucleotides are excised and repaired by the ribonucleotide excision repair machinery, including RNase H2. Kunkel, Lujan, and the rest of the team hypothesized that the incorporation and repair of the ribonucleotides pinpoints the newly copied leading strand for repair.

Using the budding yeast *Saccharomyces cerevisiae*, Lujan demonstrated that, in the absence of RNase H2, the rate of mismatch repair is reduced specifically on the leading strand. Interestingly, reducing the number of ribonucleotides incorporated into the DNA strand diminished the impact of ribonucleotide excision repair on the proficiency of mismatch repair. As Lujan concluded, “Both the number and repair of ribonucleotides affect the mismatch repair efficiency on the leading strand.”

Study marks a first in mismatch repair research

This study presents the first in vivo evidence for a signal that specifically marks the leading strand in eukaryotes. As Kunkel remarked, “Scott’s study and a parallel study published at the same time by Josef Jiricny, of the University of Zurich, and colleagues, give us a better understanding of how this machinery knows which partner in a mismatch is the mistake that needs to be removed. This is important, because the consequences of making the wrong choice are mutations that can have a variety of adverse health consequences.”

Citation: Ghodgaonkar MM, Lazzaro F, Olivera-Pimentel M, Artola-Borán M, Cejka P, Reijns MA, Jackson AP, Plevani P, Muzi-Falconi M, Jiricny J. (<http://www.ncbi.nlm.nih.gov/pubmed/23603115?dopt=Abstract>) 2013. Ribonucleotides misincorporated into DNA act as strand-discrimination signals in eukaryotic mismatch repair. *Mol Cell* 50(3):323-332.



First author Lujan is a postdoctoral fellow in Kunkel’s group. (Photo courtesy of Scott Lujan)

Linking DNA repair to human disease

There is a high degree of conservation in mismatch repair among eukaryotes. In fact, mutations in the mismatch repair machinery lead to a predisposition for cancer and, specifically, Lynch syndrome, a genetic condition that greatly increases the risk of colon cancer. Further, mutations in RNase H2 cause Aicardi–Goutières syndrome, a congenital immune-mediated neurodevelopmental disorder that is generally fatal within the first few years of life. From these pioneering studies on DNA repair mechanisms, researchers have gained new insights that are potentially relevant to the etiology and treatment of a number of human diseases.

Citation: Lujan SA, Williams JS, Clausen AR, Clark AB, Kunkel TA. (<http://www.ncbi.nlm.nih.gov/pubmed/23603118>) 2013. Ribonucleotides are signals for mismatch repair of leading-strand replication errors. *Mol Cell* 50(3):437-443.

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Kunkel holds appointments in the NIEHS Laboratory of Molecular Genetics and Laboratory of Structural Biology, where he formerly served as chief. (Photo courtesy of Steve McCaw)

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