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Scientists uncover novel role for DNA repair protein linked to cancer

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Tufts University researchers in the School of Arts and Sciences have pinpointed a key cellular protein that repairs damaged DNA molecules but may also promote the development of cancer.

Assistant Professor of Biology Mitch McVey and his research team report that DNA polymerase theta, or PolQ, promotes an inaccurate repair process, which can ultimately cause mutations, cell death or cancer. The research is published in the July 1 edition of the open-access journal PLoS Genetics.

"Although scientists have known for several years that the PolQ protein is somehow related to the development of cancer, its exact cellular role has been difficult to pin down," says McVey."Our finding that it acts during inaccurate DNA repair could have implications for biologists who study genomic changes associated with cancer."

DNA is a double stranded molecule shaped like a spiral staircase. Its two strands are linked together by nucleotides -- guanine, cytosine, adenine and thymine -- that naturally complement one another. Under normal conditions, a guanine matches with a cytosine, and an adenine with a thymine.

How DNA Double-Strand Breaks Are Repaired

But during the course of a cell's life, the staircase can become severed

into two molecules. These breaks must be repaired if the cells are to accurately replicate and pass on their genetic material. Most breaks are quickly and accurately fixed during the process of homologous recombination (HR), which uses an intact copy of DNA as a template for repair.

However, there is a second, error-prone process called end-joining repair. Here, the broken, double-stranded ends are stitched back together without regard to the original sequence. The ends of the broken strands may be altered by removal or addition of small DNA segments, which can change the genomic architecture.

In a previous paper, McVey and doctoral student Amy Marie Yu were able to demonstrate an alternative form of end-joining by studying how repair proceeds in the absence of DNA ligase 4, an important protein that links together two broken DNA ends.

After analyzing hundreds of inaccurately repaired breaks in the fruit fly Drosophila melanogaster the scientists observed two things. One, extra nucleotides were often inserted into the DNA strands at the point of the break. Second, the insertions were closely related to the original DNA sequences directly adjacent to the break.

Polymerase Theta's Role in DNA Repair and Cancer

In the current *PLoS Genetics* paper, McVey, Yu and undergraduate Sze Ham Chan showed that polymerase theta plays a dominant role in this alternative repair process. First, it reads the genetic material in DNA adjacent to the break and makes a copy of it. The newly copied DNA can then be used as a molecular splint that holds the broken ends together until they can be permanently joined. In addition, the scientists speculated that the PolQ protein also has the ability to unwind DNA sequences near a break, thereby facilitating alternative end-joining.

Other research groups have previously shown that levels of the PolQ protein are higher in several types of human tumors. McVey and his team are currently working to determine if a PolQ-dependent type of alternative end-joining is involved in the development of cancer in people. If this is indeed the case, the PolQ protein could represent a novel target for the development of new cancer drugs.

"Our first goal is to determine which parts of PolQ are required for its role in alternative end-joining," McVey says. "This will give us a road map for determining how its activity might be altered in a clinical setting."

More information: Chan SH, Yu AM, McVey M (2010) "Dual Roles for DNA Polymerase Theta in Alternative EndJoining Repair of Double-Strand Breaks in Drosophila." PLoS Genet 6(7): e1001005. doi:10.1371/journal.pgen.1001005

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