First glimpse of end-of chromosome repair in real time

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Researchers have developed a first-of-its- kind system to observe repair to broken DNA in newly synthesized telomeres, an effort which has implications for designing new cancer drugs.

Maintaining the ends of chromosomes, called telomeres, allows cells to continuously divide and achieve immortality. "Telomeres are much like the plastic cap on the ends of shoelaces—they keep the ends of DNA from fraying," said Roger Greenberg, MD, PhD, an associate professor of Cancer Biology in the Perelman School of Medicine at the University of Pennsylvania. In a new study published this week in *Nature*, senior author Greenberg and colleagues have developed a first-of-its- kind system to observe repair to broken DNA in newly synthesized telomeres, an effort which has implications for designing new cancer drugs.

Telomeres stay intact in most cancer cell types by means of a specialized enzyme called telomerase that adds the repetitive telomere DNA sequences to the ends of chromosomes. Cancer cells can also use a second method involving a DNA-repair-based mechanism, called alternative lengthening of telomeres, or ALT for short. In general, cancer cells take over either type of telomere maintenance machinery to become immortal. Overall, about fifteen percent of cancers (those of cartilage, bone, and brain, for example) use the ALT process for telomere lengthening and maintenance.

When DNA breaks, it triggers DNA repair proteins like the breast cancer suppressor proteins BRCA1 and BRCA2 into action, along with other helper proteins, that attach to the damaged stretch of DNA. These proteins stretch out the DNA, allowing it to be recognized by complementary sequences of telomere DNA. In general, this mechanism, called homologous recombination, happens when DNA building blocks are exchanged between two nearly identical molecules of DNA.

In the current Nature study, the team found that telomeres use a unique type of repair to make new DNA, which they call "break-induced telomere synthesis." The team found that the homologous recombination for telomeres was different from other forms of homologous recombination that involve BRCA1, 2 and Rad51 proteins, which are mutated in people with breast cancer and at risk for breast cancer.

"This is what we want to stop in cancer cells, but it has not been possible to directly follow the process while it is happening" Greenberg said. "This is the first study to follow all of the major steps of homologous recombination in real time. Now there is a possibility that because we know this process better, different points in the process could be interfered with to keep telomeres in cancer cells from continually lengthening. This may push them over the edge to cell death."," Greenberg said.

Essential contributions to the study came from first and second authors Robert L. Dilley and Priyanka Verma, along with coauthors Nam Woo Cho, Harrison D. Winters, Anne R. Wondisford, from the department of Cancer Biology at Penn. Greenberg is also an associate investigator at the Abramson Family Cancer Research Institute and director of Basic Science for the Basser Research Center for BRCA.

More information: Break-induced telomere synthesis underlies alternative telomere maintenance, *Nature*, nature.com/articles/doi:10.1038/nature20099

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