MedicalXpress

How the ends of chromosomes are maintained for cancer cell immortality

September 25 2014

Maintaining the ends of chromosomes, called telomeres, is a requisite feature of cells that are able to continuously divide and also a hallmark of human cancer. "Telomeres are much like the plastic cap on the ends of shoelaces—they keep the ends of DNA from fraying," says Roger Greenberg, MD, PhD, associate professor of Cancer Biology in the Perelman School of Medicine at the University of Pennsylvania. In a new study published this week in *Cell*, he and his colleagues describe a mechanism for how cancer cells take over one of the processes for telomere maintenance to gain an infinite lifespan.

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, approximately fifteen percent of cancers use the ALT process for telomere lengthening, but some cancer types use ALT up to 40 to 50 percent of the time.

Greenberg's co-authors of the new findings are Nam Woo Cho and Robert L. Dilley, both MD/PhD students in his lab, and Michael A. Lampson, an associate professor of 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.

Going Fishing

The team showed that when DNA breaks, it triggers DNA repair proteins like the breast cancer suppressor protein 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 search for complementary sequences of telomere DNA. Breast cancer is linked to mutations in the BRCA1 and BRCA2 genes and mutations in several genes involved in BRCA-related pathways have also been associated with breast cancer susceptibility. Breast and ovarian cancers are associated with a breakdown in the DNA repair systems involving these BRCA and other related proteins.

"This process of repair triggers the movement and clustering of telomeres like fish being reeled toward an angler," explains Greenberg. "The broken telomeres use a telomere on a different chromosome – the homologous telomere—as a template for repair." In fact, in cancer cells that use ALT to maintain their telomeres, the team could visualize this process by imaging these clusters of telomeres coming together.

"We are very excited about the data as it has provided new insights into this mechanism of telomere maintenance and ways to think about BRCA dependent and independent DNA recombination," he says. "But, as with most scientific studies, many more questions are raised than answers provided."

The team would like to find other proteins involved in ALT and look for small molecule drugs that target this telomere maintenance mechanism in cancer cells to selectively kill cancer types that use ALT.

Provided by University of Pennsylvania School of Medicine