Proteins that work at the ends of DNA could provide cancer insight

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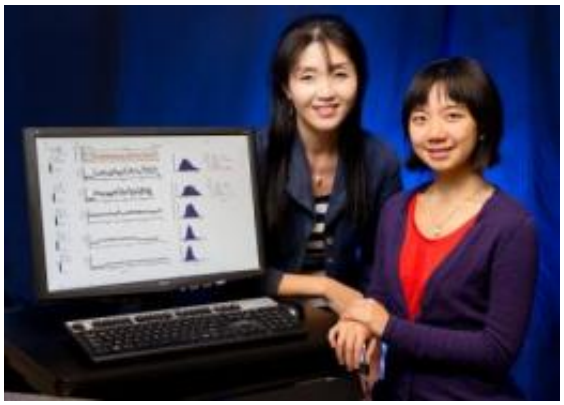

Researchers from the University of Illinois -- professor Sua Myong, left, and graduate student Helen Hwang -- determined the action of proteins that regulate the caps on the ends of DNA strands, creating an assay that could be used to screen anti-cancer drugs. Credit: L. Brian Stauffer

(Medical Xpress)—New insights into a protein complex that regulates the very tips of chromosomes could improve methods of screening anti-cancer drugs.

Led by bioengineering professor Sua Myong, the research group's findings are published in the journal *Structure*.

Myong's group focused on understanding the proteins that protect and regulate telomeres, segments of repeating DNA units that cap the ends of chromosomes. Telomeres protect the important gene-coding sections of DNA from loss or damage, the genetic equivalent of aglets – the covering at the tips of shoelaces that keep the ends of the laces from unraveling or fraying.

Telomeres play an important role in cell aging and death, since each time a cell divides, a little bit is lost from the end of the telomere. Thus, cell biologists postulate that telomere length can determine the lifespan of a cell. Cancer cells, however, have a way to get around this limitation: An enzyme called telomerase that adds length to telomeres is highly active in cancer cells. This allows cancer cells to divide in perpetuity, running amok through tissues and systems.

"Cancer researchers want to get a hold of this problem, control this indefinite lengthening of the telomeres," said Myong, who also is affiliated with the Institute for Genomic Biology at the U. of I. "A lot of the anti-cancer drugs are targeted directly to these telomeres so that they can inhibit telomerase activity. The proteins we study regulate the activity of telomerase."

Using a technique developed at Illinois that allows researchers to watch single molecules interact in real time, Myong's group determined how two proteins called POT-1 and TTP-1 bind to the telomere. POT-1 protects the fragile telomere ends from being attacked by other regulatory proteins that might mistake the end for a broken or damaged area of DNA. When POT-1 and TTP-1 work together in a complex, they promote telomerase activity, an interesting target for cancer researchers.

The group found that on its own, POT-1 binds to the folded-up telomere in distinct steps at particular points in the telomere's DNA sequence, unfolding the telomere in a stepwise manner. However, the POT-1/TTP-1 complex surprised the researchers by binding, then freely sliding back and forth along the telomere end.

"Instead of stepwise binding, what we saw was a mobile protein complex, a dynamic sliding motion," Myong said. "Somehow it was as if the static binding activity of POT-1 is completely lost – the protein complex just slid back and forth. We were able to reproduce the data and confirm it with many different tail lengths of the telomeric DNA and we know now that the contact between POT-1 and the

telomere is somehow altered when the partner protein comes and binds."

Next, the researchers will add telomerase and see how the sliding activity of the POT-1/TTP-1 complex affects telomerase activity. Myong postulates that the sliding may promote telomerase activity – and thus telomere lengthening – by making the end of the telomere accessible for the telomerase enzyme to bind.

"We are excited about the possibility that this kind of mobility can increase the telomerase extension activity," Myong said. "It's somehow engaging the enzyme so that it can stay bound to the DNA longer. So it must involve a direct interaction."

Ultimately, understanding the POT-1/TTP-1 complex gives drug developers a new target for anti-cancer drugs, and the assay Myong's group used to monitor the complex could offer a venue for evaluating telomere-targeting drugs.

"We want to extend our a basic science knowledge in telomere biology into causes of cancer and we hope that our assay can be useful for telomere -targeted drug screening," Myong said.

More information: The paper, "POT1-TPP1 Regulates Telomeric Overhang Structural Dynamics'" is available online: www.sciencedirect.com/science/ … ii/S0969212612003000

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