Study identifies a key molecular switch for telomere extension by telomerase

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Researchers at the University of Illinois at Chicago College of Medicine describe for the first time a key target of DNA damage checkpoint enzymes that must be chemically modified to enable stable maintenance of chromosome ends by telomerase, an enzyme thought to play a key role in cancer and aging.

Their findings are reported online in Nature Structural and Molecular Biology.

Telomeres are the natural ends of chromosomes, consisting of specialized DNA-and-protein structures that protect chromosome ends and ensure faithful duplication of chromosomes in actively dividing cells. An essential player in telomere maintenance is an enzyme complex called telomerase. Without telomerase, telomeres become progressively shorter each time the cell divides.

If telomeres become too short, chromosome ends will be recognized as broken, prompting DNA-damage checkpoint proteins to halt cell division and DNA repair proteins to fuse or rearrange the chromosome ends. Telomere dysfunction has been linked to tumor formation and premature aging in humans.

The UIC study, led by Toru Nakamura, associate professor of biochemistry and molecular genetics, focused on understanding how two DNA-damage checkpoint enzymes called ATM and ATR contribute to the regulation of telomerase.

"Our current study found that ATM and ATR help to switch on the telomere complex by chemically modifying a specific target protein bound to telomeric DNA, which then attracts telomerase, much like honey bees are attracted if flowers open and show bright colors," Nakamura said.

The study was done in fission yeast cells, a model organism that utilizes very similar protein complexes as human cells do to maintain telomeres. Previous discoveries in fission yeast have provided key information that helped identify several key factors required in maintenance of human telomeres.

Nakamura thinks that a similar ATM/ATR-dependent molecular switch may exist in human cells to regulate telomere maintenance. However, certain details of the protective complex regulation may be different, he noted.

Because deregulation of telomere maintenance mechanisms is a key event in tumor formation, understanding how cellular components collaborate to generate functional telomeres may be important to finding ways to prevent cancer, Nakamura said.

Provided by University of Illinois at Chicago