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Researcher defines proteins that distinguish chromosome ends from DNA double-strand breaks

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Peter Baumann, Ph.D., Assistant Investigator, and Nancy Bae, Ph.D., Postdoctoral Research Associate in the Baumann Lab, have published a paper offering insight into the way cells protect chromosome ends from misguided repair.

Published in tomorrow's issue of *Molecular Cell*, their paper entitled "A RAP1/TRF2 Complex Inhibits Non-Homologous End Joining at Human Telomeric DNA Ends" employed a biochemical assay for double-strand break repair to define the minimal requirements for the protection of telomeric DNA at the ends of chromosomes.

"Surprisingly, we found that neither long single-stranded overhangs nor t-loop formation is essential to prevent illegitimate repair of telomeric ends," said Dr. Bae. "Instead, a short tandem array of telomeric repeats bound by a Rap1/Trf2 complex is sufficient to impede non-homologous end joining in a highly directional manner."

It has long been understood that chromosome ends are distinct from DNA double-strand breaks and that the cellular machinery that repairs DNA breaks does not act on telomeres. But how repair factors are prevented from acting at chromosome ends has been a hotly debated issue. Over the past decade, several telomeric complexes and structures have been identified and proposed to protect chromosome ends, but conclusive evidence that any of these are required for protection has

been lacking.

"We set out to define the minimal requirements that would allow the DNA repair machinery to distinguish a chromosome end from a break," said Dr. Baumann. "By establishing an in vitro assay for chromosome end protection and by implicating specific proteins, we have opened the door to elucidate the mechanism by which RAP1/TRF2 inhibits double-strand break repair at chromosome ends."

"These findings are important for establishing a better understanding of tumor development," said Robb Krumlauf, Ph.D., Scientific Director. "Genomic instability and gross chromosomal rearrangements are a hallmark of cancer cells. The mechanisms that initiate and drive these events are only poorly understood, but it is widely accepted that loss of chromosome end protection can initiate genomic instability through bridge-breakage-fusion cycles. It is, therefore, very important to understand the mechanism of chromosome end protection and how and why it fails during tumorigenesis."

Source: Stowers Institute for Medical Research