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Study in roundworm chromosomes may offer new clues to tumor genome development

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A study of DNA rearrangements in roundworm chromosomes may offer new insight into large-scale genome duplications that occur in developing tumors.

A report of the research led by University of North Carolina at Chapel Hill School of Medicine scientists was published in the April 22 online edition of the journal *Science*. The study focused on telomeres, a region of repetitive DNA sequence that protects the ends of chromosomes from deterioration or from fusing with other chromosomes.

In many organisms, including humans, chromosome ends are capped by simple repetitive sequences that are replenished by addition of new telomere repeats by the enzyme telomerase. Since most human cells don't produce enough of the enzyme, they are unable to maintain the repeat DNA sequences that cap their chromosome ends.

"Once telomere repeat sequences erode completely, a chromosome end will 'uncap' and fuse with another uncapped chromosome end," said senior study author Shawn Ahmed, PhD, associate professor of genetics and a member of the UNC Lineberger Comprehensive Cancer Center. "Thus, the chromosome aberrations that we isolated from telomerase mutants in the common roundworm C. elegans were end-to-end chromosome fusions."

Ahmed points out that during development of many forms of cancer, chromosome ends erode and 'uncap', and many end-to-end chromosome

fusions occur. These fusions create genome rearrangements that may contribute to tumor development.

The new findings tested predictions of a long-standing model developed in the 1940s by geneticist Barbara McClintock, 1983 Nobel Laurate in Physiology or Medicine. This model, termed the breakage-fusion-bridge cycle, suggested that DNA duplications at fused chromosome ends should be perfect inverted duplications that are created by fusion and then breakage of a fused chromosome during the process of cell division, mitosis.

"Surprisingly, many of the duplications that we studied were 'interrupted' by deletions as well as single copy, three copy and four copy segments of DNA. In addition, some duplications were created by events that copy DNA by hopping backwards and forwards along a chromosome," Ahmed said. "These observations defy predictions of the breakage-fusion-bridge cycle and suggest that an alternative model: a promiscuous DNA replication process may be responsible for creating duplications at fused chromosome ends."

The researcher adds: "Similar interrupted duplications have been observed for segments of the human genome that spontaneously duplicate to cause inherited diseases. So, the duplications that we observe at fused chromosome ends may be created by a 'general' duplication mechanism.

"Our study provides a blueprint for solving structures of analogous chromosome rearrangements that may occur frequently in tumor genomes, many of which are currently being sequenced."

UNC study co-author is Mia Rochelle Lowden, a former PhD student and postdoctoral researcher in the departments of genetics and biology. Other collaborators are Stephane Flibotte, PhD and Donald Moerman,

PhD, department of zoology in the University of British Columbia, Canada.

Provided by University of North Carolina School of Medicine