Dual systems key to keeping chromosomes intact

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USC scientists have discovered how two different structural apparatuses collaborate to protect repetitive DNA when it is at its most vulnerable – while it is being unzipped for replication.

The centromere—the center of the "X" shape of a chromosome—contains repeated DNA sequences that are epigenetically coded to attract so-called heterochromatin proteins. This protects the structure to ensure that the chromosomes separate properly. If the heterochromatin is lost (due to mutations in the cell), the repetitive DNA becomes vulnerable to rearrangements and recombination. This particularly true during DNA replication, when the DNA is transiently unwound to be copied.

If there are also defects in replication fork proteins that cause this process to be delayed or inefficient, the rearrangements are dramatically increased. This "genome instability" can lead to loss of genetic information or genetic changes that can lead to cell death or cause cancer.

Susan Forsburg, who led the USC team that conducted the research, used yeast cells to show that simultaneously disrupting both heterochromatin and replication fork proteins caused significant increases in abnormal chromosomes, and in some cases, cell death.

"The insight here is really understanding the mechanism of how these different mutants create a lethal collaboration," said Forburg, a professor

of molecular biology at the USC Dornsife College of Letters, Arts and Sciences. "Importantly, all the genes we study have human equivalents—and mutations of some of these are already linked to cancer."

The research appears online in *Cell Reports* on March 7. Forsburg worked with Pao-Chen Li, formerly a graduate student at USC and now a post-doctoral researcher at UCSF; as well as Ruben C. Petreaca, Amanda Jensen, Ji-Ping Yuan and Marc D. Green, all from USC.

"We already knew epigenetic modifications change gene expression in cancer," Forsburg said. "Now we see a synergistic effect between the structural role of epigenetic modification that creates heterocrhomatin, and replication fork stability."

The next step will be to identify additional components that show this same synergistic effect and to determine what other functions act with heterochromatin to preserve genome stability.

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