Study Confirms DNA Repair Model After 26 Years

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(PhysOrg.com) -- UC Davis researchers have confirmed a central idea about chromosome repair, more than a quarter century after it was first proposed. The finding is important to scientists who seek to understand DNA repair, a vital process in preventing cancer and birth defects.

Malgosia Bzymek, a research scientist in the UC Davis Department of Microbiology, and her colleagues showed that a DNA structure called the double-Holliday junction can form when growing body cells repair a broken chromosome by a process called homologous recombination. Their study appears in the April 8 issue of the journal *Nature*.

“For 26 years we have assumed that double-Holliday junctions are intermediates of DNA break repair, but actually identifying these structures in cells has been impossible until now,” said Neil Hunter, associate professor of microbiology at UC Davis and senior author of the paper. “We now have a powerful new tool to investigate this area."

Holliday junctions form when a broken chromosome uses the matching DNA on another chromosome as a template for repair. As the two chromosomes interact they form four-stranded X-shape structures -- the Holliday junctions -- that can resolve in two different ways: by a ‘crossover’ that swaps strands between chromosomes, or by restoring the original strands.

In addition to identifying the elusive double-Holliday junctions, Bzymek and colleagues also observed striking differences in different cell types.

In cells undergoing the sexual cell division process called meiosis, there are lots of double-Holliday junctions and lots of crossovers. But in cells dividing by mitosis, double-Holliday junctions form infrequently during chromosome repair and crossovers are similarly rare.

In meiosis, a cell divides twice to produce sperm and egg cells with a single copy of each chromosome. The “magic of meiosis” occurs when parental chromosomes, from mom and dad, associate in pairs, become connected by crossovers and then separate away from each other at the first division. “Crossovers are at the heart of this process; without the connections they provide, mom and dad chromosomes are often pulled in the same direction, and the resulting sperm or eggs have odd numbers of chromosomes,” Hunter said.

In mitosis, the process that creates and replaces most of the body's cells, a cell splits into two identical daughters. Before a cell divides, its chromosomes must be completely and accurately copied. Homologous recombination helps fix breaks that arise during DNA replication.

"It makes sense that the double-Holliday junction pathway is a minor pathway of break repair in mitotically dividing cells because it is more likely to result in a crossover, and crossovers can cause the types of genetic changes that lead to cancer," Hunter said.

Co-authors of the study were Nathaniel Thayer, a UC Davis undergraduate and now a graduate student at the University of Washington; Steven Oh, a UC Davis graduate student now a postdoctoral fellow at UCSF; and Professor Nancy Kleckner of Harvard University. The work was supported by the National Institutes of Health and the Howard Hughes Medical Institute.

Provided by UC Davis