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Biologists describe mechanism promoting multiple DNA mutations

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DNA mutations—long known to fuel cancer as well as evolutionary changes in a living organism—had been thought to be rare events that occur randomly throughout the genome.

However, recent studies have shown that cancer development frequently involves the formation of multiple mutations that arise simultaneously and in close proximity to each other. These groups of clustered mutations are frequently found in regions where chromosomal rearrangements take place.

The discovery, published in the journal *Cell Reports*, may one day lead to new cancer therapies, according to a University of Iowa biologist and her colleagues, and a group of researchers from the National Institute of Environmental Health Sciences led by Senior Associate Scientist Dmitry Gordenin.

The formation of clustered mutations may result from the process of DNA repair.

Anna Malkova, associate professor of biology in the UI College of Liberal Arts and Sciences, notes that the DNA repair pathway, known as break-induced replication (BIR), can promote clusters of DNA mutations.

"Previously, we have shown that double-strand DNA breaks, which can result from oxidation, ionizing radiation and replication errors, can be

repaired by BIR," says Malkova.

"During BIR, one broken DNA end is paired with an identical DNA sequence on another chromosome and initiates an unusual type of replication, which proceeds as a migrating bubble and is associated with the accumulation of large amounts of single-strand DNA," she says.

In the *Cell Reports* study, researchers subjected yeast cells undergoing BIR to alkylating (cancer cell-killing agents) damage. "We found that the single-stranded DNA regions that accumulate during BIR are susceptible to damage that leads to the formation of mutation clusters," explains Cynthia Sakofsky, postdoctoral fellow at the UI and one of two co-first authors on the paper. "These clusters are similar to those found in human cancer," she says.

Importantly, say the researchers, the paper provides a mechanism to potentially explain how genetic changes form in human cancers. Thus, it will be critical for future research to determine whether BIR can form clustered mutations that lead to cancer in humans. If this turns out to be true, it may lead to the discovery of new targets for developing therapies against human cancers.

Provided by University of Iowa