Ancient proteins involved in DNA repair could shed light on tumor development

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A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

By studying the yeast used in beer- and bread-making, researchers at the University of Pittsburgh School of Medicine have uncovered the mechanism by which ancient proteins repair DNA damage and how their dysfunction could lead to the development of tumors. The findings, published online today in *Nature Communications*, could lead to new ways to tailor cancer therapies.

In humans, protein mutations called RAD51 paralogues have been associated with breast and ovarian tumors, said senior investigator Kara Bernstein, Ph.D., assistant professor of microbiology and molecular genetics at Pitt School of Medicine and the University of Pittsburgh Cancer Institute, partner with UPMC CancerCenter.

"These are proteins that have been present throughout evolution in many species, but very little has been known about what they do," she said. "Our study shows for the first time the mechanism of how they are involved in the repair of damaged DNA."

Because RAD51 paralogues are too difficult to work with in animal cells, the research team instead explored their function in yeast. They found the proteins interact with other proteins called the Shu complex to repair breaks in DNA strands, which can be caused by environmental toxins, radiation and other naturally occurring exposures.

Shu complex works synergistically with additional RAD51 paralogues to search for homologous, or complementary, DNA regions with double-strand breaks, in which both poles of the twisting DNA ladder have been broken, the researchers found. Pieces of the genetic code can be lost in such areas; the paralogues and complex repair the damage by filling in the missing pieces in a process called homologous recombination.

"Now that we understand what the proteins do, we can perhaps tailor therapies for patients who have cancer and mutations in these repair

genes," Dr. Bernstein said.

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