MedicalXpress

DNA discovery opens new door to develop tools, therapies for hereditary cancers (w/ Video)

July 8 2010

By solving the three-dimensional structure of a protein involved in repairing DNA errors, a group of McMaster University researchers have revealed new avenues to develop assessment tools and alternative treatments for people living with hereditary colorectal cancers.

The finding, published in the journal *Molecular Cell*, is an important step forward in the field of molecular and structural biology. The McMaster researchers uncovered how a specific protein, known as MutL, works within a cell to unleash the series of events that repair DNA when the replication machinery makes a mistake.

The research team was led by Alba Guarné, an associate professor in the Department of Biochemistry and Biomedical Sciences at McMaster, and involved researchers in Europe and the United States. The lead author of the study was Monica Pillon, a master's student in the Guarné laboratory.

Errors in DNA can arise from many types of damage including external harm, such as UV radiation or carcinogens, as well as by intrinsic cellular processes such as DNA replication. Failure to correct these errors leads to mutations, which results in cancer or a number of severe genetic disorders.

To prevent this from happening, cells posses a variety of DNA repair systems that correct these errors or trigger cell death when the damage

cannot be fixed.

In this study, the investigators examined the DNA mismatch repair pathway, which corrects errors that have escaped proofreading during DNA replication. Specifically, they examined the protein MutL - a matchmaker protein - that recruits other enzymes and proteins within the cell to recognize, remove and correct mismatched DNA.

Research has shown that mutations on the genes that encode mismatch repair proteins give rise to two forms of familial cancer - hereditary non-polyposis colorectal cancer and Turcot Syndrome, which is associated with colorectal cancer as well as very aggressive brain tumours.

"The reason why it can lead to cancer is because if you don't have mismatch repair proteins that correct these errors, you're going to accumulate mutations," said Guarné. "People with defective mismatch repair genes develop cancers at very early ages. You would see a family that in their 30s has colorectal cancer and in their 40s they have it again. There's no way you can prevent that - you can't correct your DNA. As you grow older, you're going to accumulate mutations."

To determine how MutL is regulated, the researchers characterized the functional and structural domain of the protein that is involved in DNA mismatch repair. By mapping out MutL, they were able to unveil how the replication machinery turns MutL into an enzyme that cuts the error from the DNA. They also discovered that PCNA, another protein within the pathway, allows DNA to bind to MutL so it can be repaired.

"This is especially important because we've known for more than a decade that the PCNA protein is necessary to correct mismatches, but we didn't know its concrete function," Guarné said. "We're starting to understand that one of the roles of these replication proteins is to license the cutting activity of MutL."

The findings have profound implications in understanding the molecular mechanisms that predispose to cancer and Turcot syndrome development. In particular, it allows scientists to pinpoint mutations on the MutL protein in order to determine severity and long-term outcomes.

The results also provide new avenues to develop alternative cancer treatments, as the hope is future cancer therapies may be focused at the molecular level and involve blocking specific pathways within the cell.

More information: The research appears in the July 9 print issue of Molecular Cell.

Provided by McMaster University