New molecule identified in DNA damage response

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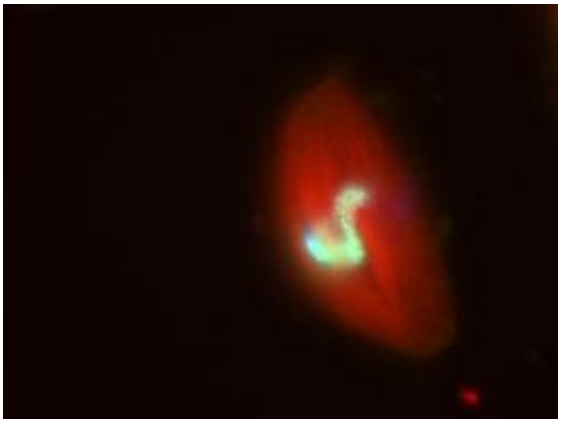

Stabilizing DNA. Researchers have identified the molecule SMARCAL1 as involved in cells' elaborate system for recognizing and repairing DNA damage during cell division. The protein is pictured above (green) in the presence of DNA (blue) as the chromosomes align along the mitotic spindle (red).

(PhysOrg.com) -- Evolution places the highest premium on reproduction, natural selection's only standard for biological success. In the case of replicating cells, life spares no expense to ensure that the offspring is a faithful copy of the parent. Researchers have identified a new player in this elaborate system of quality control, a gene whose mutation can cause a rare but lethal disease.

In the harsh judgment of natural selection, the ultimate measure of success is reproduction. So it's no surprise that life spends lavish

resources on this feat, whether in the courtship behavior of birds and bees or replicating the cells that keep them alive. Now research has identified a new piece in an elaborate system to help guarantee fidelity in the reproduction of cells, preventing potentially lethal mutations in the process.

In experiments to be published in the December 18 issue of the *Journal of Biological Chemistry*, researchers at The Rockefeller University identified the molecule SMARCAL1 as part of cells' damage control response to malfunctioning DNA replication. In typical cell division, many different molecules have roles in guaranteeing the daughter strands of DNA are as identical as possible to their parent. Some molecules check for errors or 'proofread' the offspring for typos, for instance; others, when alerted to a problem, arrest the replication process and conduct repairs.

Lisa Postow, a postdoctoral fellow in Hironori Funabiki's Laboratory of Chromosome and Cell Biology, used mass spectroscopy to identify SMARCAL1 as involved in this intricate quality control process. Working with Brian T. Chait's Laboratory of Mass Spectrometry and Gaseous Ion Chemistry, Postow found the protein in a proteomics screen for molecules that were drawn to a dangerous DNA repair problem called a double-strand break.

In both human cells and in cells from African clawed frog egg extract, Postow found that at double-strand breaks, SMARCAL1 gathered with another molecule called RPA, which is known to coat broken strands of DNA and protect them while damage is repaired. SMARCAL1 had an added interest, too: A mutation in the gene that produces it is involved in a rare but lethal disease called Schimke immuno-osseous dysplasia, a disorder that causes wide-ranging problems including kidney malfunction, immunodeficiency and growth inhibition.

To Postow's surprise, she found that removing SMARCAL1 had little effect on double-strand break repair. However, it did facilitate a different aspect of the DNA damage response called replication fork stabilization, a process that holds steady the junction between parental and daughter strands — the replication fork — when replication is stalled because a problem has been detected. "For a mutation that causes such wide-ranging and severe physiological effects, it is surprising that the protein has such a relatively small effect at the cellular level," Postow says.

Postow's findings were largely corroborated by independent new research into SMARCAL1, which was published this fall in four back-to-back papers in Genes & Development. The work reveals another piece of the complex safeguards the body has in place to protect against dangerous mutations.

"This study also proves that the proteomic approach that Lisa has developed with Dr. Chait can efficiently identify proteins involving the DNA-damage recognition and repair process," says Funabiki. "Many more excitements are ahead of us."

More information: Journal of Biological Chemistry online: October 19, 2009, Identification of SMARCAL1 as a component of the DNA damage response, Lisa Postow, Eileen M. Woo, Brian T. Chait and Hironori Funabiki

Provided by Rockefeller University (news : web)