Two proteins act as molecular tailors in DNA repair

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(PhysOrg.com) -- On average, our cells encounter a very lethal form of DNA damage 10 times a day. Lucky for us, we have the capacity to repair each and every one of them. New research now reveals exactly how two well-known proteins are involved in the process, a finding that not only helps shed light on cancer but also on how our cells maintain the integrity of our genome.

Every day tiny segments of our DNA are chipped or fragmented or get stuck together when they should really be pulled apart. But what our genome necessarily lacks in stability it makes up for with a phalanx of guards that monitor and repair the damage.

In new research to appear in this week's advance online issue of *Science*, researchers at Rockefeller University and Harvard Medical School have pinpointed the role that two well-known proteins play in the repair of one of the most lethal types of DNA damage. The damage, known as inter-strand crosslinks, occurs when the two strands of the double helix are linked together, blocking replication and transcription.

"Our cells encounter, on average, 10 inter-strand crosslinks a day," says Agata Smogorzewska, head of the Laboratory of Genome Maintenance at Rockefeller University. "We suspected that these two proteins directly participated in the repair process. Until now, we knew that they localized to the sites of damage but we had no idea what they were doing there. This work breaks that barrier."

The two proteins, called FANCI and FANCD2, are part of the Fanconi anemia pathway, which repairs inter-strand crosslinks. If any one of the 13 proteins in this pathway is damaged, the result is Fanconi anemia, a blood disorder that leads to bone marrow failure and leukemia, among other cancers, as well as many physiological defects.

In 2007, when Smogorzewska discovered FANCI, it was shown that the protein formed a complex with FANCD2, which is then chemically altered through a process called ubiquitylation. The chemically altered complex is then recruited to the site of the crosslink, where it joins forces with other repair molecules. Beyond these details, the researchers knew that repair involves snipping out and replacing the damaged DNA, but didn't know if FANCI and FANCD2 play a role in this molecular tailoring.

Using a specialized cell system of frog egg extracts, the researchers found that the two proteins are essential in the excision and insertion steps, providing powerful evidence that Fanconi anemia is a bona fide DNA repair disorder, explains Smogorzewska. The finding also explains why cells taken from Fanconi anemia patients die when exposed to inter-strand crosslink-inducing agents such as chemotherapy drugs.

"The beauty of this work is that we now have a system that enables us to explore the behavior of other key proteins in Fanconi anemia and form a picture of how they all work together," says Smogorzewska. "This will not only help shed light on how to fight cancer but how to maintain the stability of our genome."

More information: *Science* online: November 12, 2009, The Fanconi Anemia Pathway Promotes Replication-Dependent DNA Interstrand Cross-Link Repair, Puck Knipscheer, Markus Räschle, Agata Smogorzewska, Milica Enoiu, The Vinh Ho, Orlando D. Schärer, Stephen J. Elledge and Johannes C. Walter