MedicalXpress

New insights into DNA repair process may spur better cancer therapies

September 30 2013

By detailing a process required for repairing DNA breakage, scientists at the Duke Cancer Institute have gained a better understanding of how cells deal with the barrage of damage that can contribute to cancer and other diseases.

The insights, reported online the week of Sept. 30, 2013, in the journal *Proceedings of the National Academy of Sciences*, build on earlier work by the research team and identify new prospects for developing cancer therapies.

The researchers have focused on a complex series of events that cells routinely undertake to repair DNA damaged by sun exposure, smoking and even normal metabolism. If not correctly repaired, DNA breakages can result in cellular damage leading to cancer.

"We never had good assays to measure how DNA breaks are repaired, and there were few good tools to study how that repair unfolds at the molecular level," said senior author Michael Kastan, M.D., PhD, executive director of the Duke Cancer Institute. "Our work for the first time enables us to both sensitively measure the repair of DNA breaks and study the molecular mechanisms by which they occur."

DNA inside the cell faces a challenge for repairing itself because it is so compacted in the cell nucleus. Tightly wrapped in a complex of proteins called chromatin, the DNA is spooled like thread around a protein structure called a nucleosome. DNA could suffer a breakage that would

go unheeded if it remained deep within the reel.

The system developed by Kastan and colleagues induced DNA breakage at defined points on the DNA strands, enabling researchers to chronicle events as the cells launched the repair process.

What they described for the first time was a choreographed interaction in which the tightly wound DNA was temporarily loosened when a key protein, called nucleolin, was recruited to the breakage site, disrupting the nucleosome spool. The process was then reversed when the nucleosome was re-formed after repair was complete.

"Our study demonstrates for the first time the functional importance of nucleosome disruption in DNA repair," Kastan said. "This nucleosome disruption allows DNA repair proteins to access the DNA lesion and begin the process of mending the breakage."

Kastan said the finding provides key insights for how cells remain healthy, as well as how the repair process could potentially be manipulated. New cancer therapies, for instance, could target nucleolin to enhance sensitivity of tumor cells to radiation or chemotherapies, he said.

"This could give us an opportunity to make current treatments more potent," Kastan said. "That would be a next area of research, which we are especially interested in pursuing."

More information: Nucleolin mediates nucleosome disruption critical for DNA double-strand break repair, www.pnas.org/cgi/doi/10.1073/pnas.1306160110