MedicalXpress

Malfunction in molecular 'proofreader' prevents repair of UV-induced DNA damage

April 21 2014

Malfunctions in the molecular "proofreading" machinery, which repairs structural errors in DNA caused by ultraviolet (UV) light damage, help explain why people who have the disease xeroderma pigmentosum (XP) are at an extremely high risk for developing skin cancer, according to researchers at the University of Pittsburgh School of Medicine and the University of Pittsburgh Cancer Institute (UPCI). Their findings will be published this week in the early online version of the *Proceedings of the National Academy of Sciences*.

Previous research has shown that a DNA-repair protein called human UV-damaged DNA-binding protein, or UV-DDB, signals for a repair when two UV-DDB molecules bind to the site of the problem, said senior investigator Bennett Van Houten, Ph.D., the Richard M. Cyert Professor of Molecular Oncology, Pitt School of Medicine, and co-leader of UPCI's Molecular and Cell Biology Program.

"Our new study shows UV-DDB makes stops along the DNA strand and transiently attaches to it, causing a proofreading change in the protein's conformation, or shape. If the DNA is damaged the protein stays, if the DNA is not damaged the protein leaves," Dr. Van Houten said. "When it comes to a spot that has been damaged by UV radiation, two molecules of UV-DDB converge and stay tightly bound to the site, essentially flagging it for the attention of repair machinery."

The researchers followed the trail of single molecules of UV-DDB by tagging them with light-emitting quantum dots, enabling them to watch

the molecules jump from place to place in real time on both normal and UV-exposed DNA strands.

They also tracked a mutant UV-DDB protein associated with XP, an inherited, incurable disease of light sensitivity that affects about 1 in 250,000 people. They found that the mutant UV-DDB molecules are still capable of binding to DNA, but continued to slide along the DNA rather than staying put to signal where the fix was needed.

"Without this important damage control, UV-induced errors could accumulate to cause cell alterations that foster cancer development," Dr. Van Houten said. "Like a bus with no brakes, the XP-associated UV-DDB complex stays on the road and sees possible passengers, but keeps going past the stop."

More information: Single-molecule analysis reveals human UV-damaged DNA-binding protein (UV-DDB) dimerizes on DNA via multiple kinetic intermediates, *PNAS*, 2014. www.pnas.org/cgi/doi/10.1073/pnas.1323856111

Provided by University of Pittsburgh Schools of the Health Sciences