How a protein "cancer cop" targets UV damage in DNA

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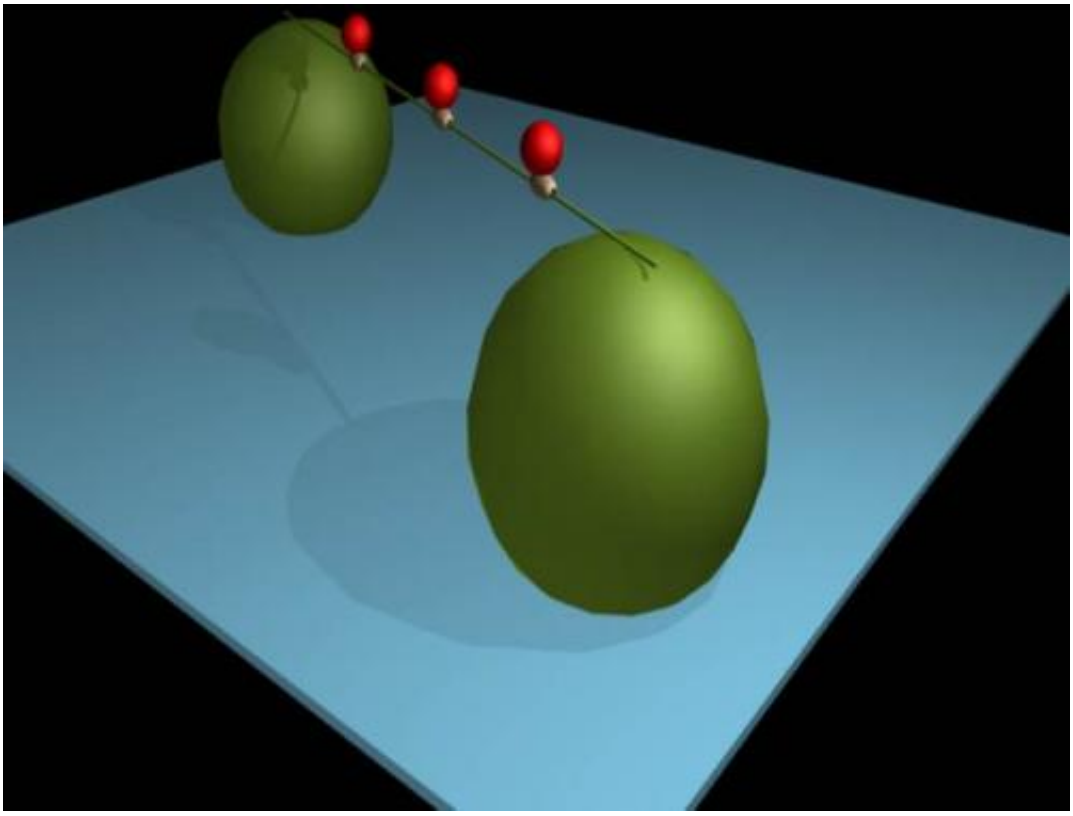

Quantum dot labeled proteins on a DNA tightrope. Image courtesy of Dr. Neil Kad.

Ah, summer. People are outside enjoying the warm weather, swimming, playing, or just soaking up that glorious, skin-damaging, high-energy UV radiation from the sun.

We know that prolonged sun exposure damages skin – the sun is a nuclear reactor, after all. But how does our body respond to and repair this damage at the DNA level?

NC State experimental biophysicist Hong Wang is a specialist in protein/DNA interactions. Recently, she was part of a team led by Dr. Bennett Van Houten of the University of Pittsburgh School of Medicine that looked at a DNA repair protein called UV-DDB (which stands for UV-damaged DNA-binding protein) and how it does its job.

UV-DDB is a policeman, and DNA is its beat. UV-DDB is constantly scanning strands of DNA looking for lesions – or sites of damage – on the strand. UV-DDB is the first protein at the scene of UV-induced DNA lesions. If these lesions aren't located and fixed they could impact a cell's ability to divide properly, leading to mutations and, over the long term, to cancer.

When UV-DDB spots a lesion, it calls for backup. A team of 20 different "first responder" proteins show up and remove the DNA lesions, allowing the cell to divide normally.

The researchers wanted to know how, exactly, UV-DDB walks its beat. In each cell, there are about 180,000 of these protein "cops," but there are several billion DNA base pairs in the human genome, so the cops have a lot of ground to cover on every strand of DNA. Plus, DNA strands are super long, so to get packed into a cell they wind themselves around clumps of histone proteins to save space. This structure makes it even harder for a UV-DDB protein to get around to all the different spots on the DNA.

Proteins can move along strands of DNA in different ways – they can slide along the strand like skateboarders grinding a rail (called a one-dimensional search), or they can jump on and off of the strand at

different points (a three-dimensional search).

To see what UV-DDB does in real time, the researchers tagged the protein with fluorescent nanoparticles called quantum dots. Quantum dots serve as molecular beacons that allow researchers to track individual UV-DDB proteins. Using a high-speed camera (20 frames per second) and a fluorescence microscope, researchers captured video of UV-DDB's movements on DNA. This technique is called single-particle tracking.

The technique revealed that UV-DDB prefers a three-dimensional search (jumping) to a one-dimensional search (sliding) when it "interrogates" the DNA for damage. That's because the 3-D search makes it easier for UV-DDB to navigate obstacles like histones and other proteins when it's searching for lesions.

Interestingly, researchers also discovered that UV-DDB proteins work with a partner when trying to find lesions in the portions of the DNA strands that wrap around histones. The two proteins form a complex structure called a dimer that makes them even more efficient at finding lesions in the wrapped portions. When a UV-DDB dimer finds a lesion, it stays put at the site for at least 15 minutes to wait for other DNA repair proteins to arrive and carry on the repair process. In contrast, a mutant version of UV-DDB that the researchers observed prefers one-dimensional sliding on DNA and cannot stably engage with lesions.

So while it's good to know that you've got cancer cops on DNA duty while you're having your day at the beach, be a good citizen and remember to enjoy the sunshine responsibly.

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