DNA strands often 'wiggle' as part of genetic repair

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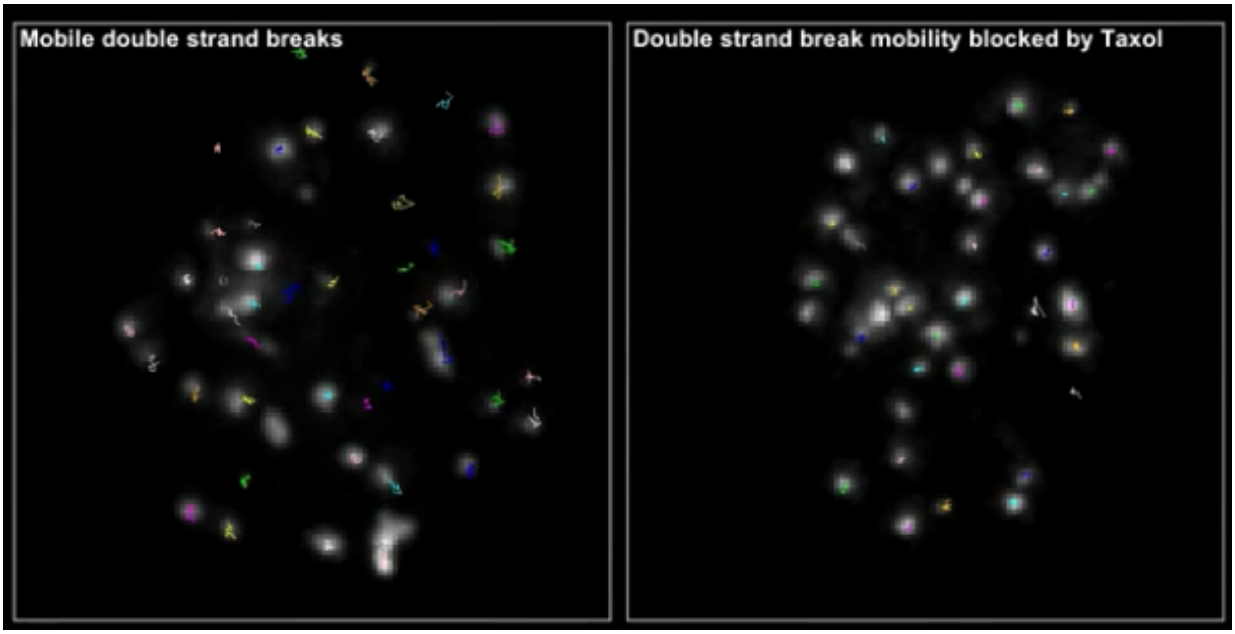

Sometimes, the molecules that make up life exhibit strange behavior. For instance, in simple organisms such as yeast, when genetic material becomes damaged, the affected DNA strands increase their motion, waving about inside the cell like a sail unfurled.

Over the years, scientists have seen more instances of such curious behavior during DNA repair—one of life's most fundamental

processes—but whether it also happened in human cells was debated. Until now.

New research by Rockefeller University scientists shows the swaying of strands is, in fact, a pervasive part of DNA repair in mammalian cells. Titia de Lange, the Leon Hess Professor and head of the Laboratory of Cell Biology and Genetics, led the study, which was described November 5 in *Cell*.

"This paper shows that an increase in physical mobility of DNA strands is something that happens inside mammalian cells every time there is a break in the DNA," says de Lange, who is also American Cancer Society Professor, and Director of the Anderson Center for Cancer Research at Rockefeller. "These breaks—and the subsequent increase in DNA mobility—can happen as a result of problems during DNA replication, chemotherapy, and other causes."

By learning more about this intriguing mechanism, the researchers hope to find new ways to optimize our use of cancer treatments, some of which act by manipulating the DNA repair process in malignant cells.

For many years, biologists hotly debated how common it was for DNA to become more mobile following damage. In 2008, de Lange and her team detected the process in telomeres, the caps on the ends of chromosomes, by filming DNA before and after damage occurred. This was a key finding, as telomeres serve important functions in cell division and protecting mammalian chromosomes.

Since that study, de Lange and postdoctoral fellow Francisca Lottersberger in her lab have identified the cellular structures involved in increasing DNA mobility after damage. One of those structures is embedded in the nuclear envelope, the barrier surrounding the chromosomes. Surprisingly, the second structure that boosts mobility in

damaged DNA—microtubules—resides outside the nucleus, in the cytoplasm. Microtubules are highly dynamic rods that can move things around inside the cell, but can also poke the nucleus. Somehow, the microtubules interact with the nuclear envelope to send a signal to increase mobility of damaged DNA.

With these discoveries, de Lange and her team had the tools to determine the pervasiveness of DNA mobility in the mammalian genome—by deleting the structures it depended upon. When the team deleted the envelope protein, double-stranded breaks in DNA throughout the genome became less mobile. The same occurred when the researchers added drugs that inhibit microtubules.

The next step, de Lange says, is to try to find out why DNA mobility increases following damage. One possibility, she proposes, is that the process serves as a "fail-safe mechanism" when normal repair processes don't work: The more the broken strands move around, the bigger the chances are of them finding each other again, and repairing the break.

But this process is dangerous when many DNA breaks occur at once—such as after exposure to chemotherapy. In this situation, the movement of broken ends can cause pieces from different chromosomes to stick together, forming monster chromosomes that kill the cell. This principle underlies the treatment of certain forms of breast and ovarian cancer with new drugs called PARP inhibitors, which cause many DNA breaks at once.

But now that de Lange has shown that microtubules are needed for this process, it points to a potential problem if doctors combine PARP inhibitors with another type of chemotherapy that is often prescribed in these cancers, Taxol (paclitaxel)—which kills cells by disrupting the function of microtubules. Without microtubules, damaged DNA ends are less mobile, and less likely to form monster chromosomes. So, the

effect of one drug may counteract the other.

"Although we are investigating a very basic problem in biology—how cells repair DNA damage —our discoveries have potential ramifications in the clinic," says de Lange.

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