Study finds crucial step in DNA repair

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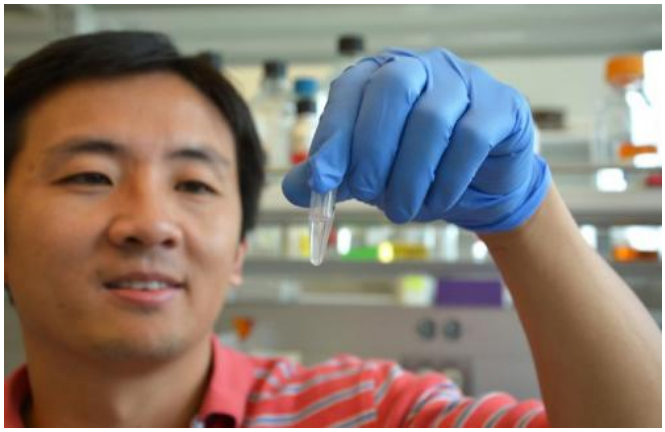

Peng Mao in his lab in the WSU School of Molecular Biosciences. Credit: Rebecca E. Phillips

Scientists at Washington State University have identified a crucial step in DNA repair that could lead to targeted gene therapy for hereditary diseases such as "children of the moon" and a common form of colon cancer.

Such disorders are caused by faulty DNA repair systems that increase the risk for cancer and other conditions.

The findings are published in this week's *Proceedings of the National Academy of Sciences*.

Regents Professor Michael Smerdon and post-doctoral researcher Peng Mao found that when DNA is damaged, a specific protein must first be "unbuckled" to allow easy access for the DNA "repair crew." Without this unbuckling, entry to the damaged site is hampered by the compact arrangement of genes and protein in chromosomes called chromatin.

Smerdon and Mao's finding is one of the first to document details of how this repair process takes place in chromatin.

Daily demands for DNA repair

Each human cell sustains a range of assaults that can create up to 100,000 DNA injuries every day, said Smerdon. The cells must repair this damage by continually—and quickly—producing replacement DNA and proteins.

Like a tiny locomotive, an enzyme called RNA polymerase runs up and down the DNA copying genetic information. When it comes to a gene whose protein is needed by the cell, it stops and unwinds the double-stranded DNA, copies one strand and sends it off to machinery to manufacture the new protein. And all is well.

But when DNA is damaged by UV radiation or harmful substances, it forms an impenetrable mass that stalls the RNA polymerase, said Smerdon. Like a boulder on the railroad tracks, the lifeless lump blocks all protein production from that gene. Unless quickly repaired, the cell could die.

In healthy people, an enzyme repair crew travels along with the RNA polymerase and instantly rushes in to excise the damage and clear the tracks. This is called transcription-coupled repair, or TCR, an aspect of one of four known DNA repair systems. Smerdon said that even a partial deficiency in any of the repair systems could lead to life-threatening disorders.

Children of the moon

Smerdon's laboratory studies repair deficiency diseases like xeroderma pigmentosum or XP, first identified as a possible hereditary disorder in 1874. Known as children of the moon, XP patients lack the enzymes to cut out damaged DNA and are so sensitive to UV light that even fluorescent lights can blister their skin.

Their skin cancer rates are 2,000 times higher than in people without the disorder. They can safely venture outside only at night.

Smerdon and his colleagues also study Cockayne Syndrome, a TCR deficiency disease that causes extreme sun sensitivity, nervous system degeneration and premature aging.

Other DNA repair deficits can cause a range of diseases such as leukemia, breast cancer and hereditary non-polyposis colorectal cancer, a common cause of colon cancer in Western nations.

Loosening the belt

Using yeast and human cells, Smerdon, Mao and their team discovered that there are two steps to the normal TCR repair process and that a protein in the chromatin, called H2B, is critically involved in the first step.

To help the repair enzymes gain entry to heavily shielded DNA, H2B first unbuckles a smaller protein. Like loosening your belt after a big dinner, this allows the strands of DNA to relax and move apart. As the strands open, the repair crew has room to come in and clear the damage.

This unbuckling of the smaller protein, ubiquitin, is saddled with a jawbreaker term called deubiquitylation, but Smerdon and Mao say it makes DNA repair more efficient and that without it repair would be next to impossible.

Their finding sets the stage for future investigations into the largely uncharted arena of DNA repair in chromatin. The goal is to better understand how this process works in humans.

Gene therapy

"Even at a basic fundamental level, I have not lost sight of what you hope this research could ultimately do in terms of human health," said Smerdon.

"One of the treatments under development is targeted gene therapy," he said. "If a patient has a mutation in a specific gene, it would be a way of giving them a normal copy to try to correct that gene. Though it has been done successfully in some diseases, it is still being investigated in repair deficit cases."

Mao speculates that in the future, people with DNA repair problems might be given a drug that could boost the activity of repair enzymes. But there are no clinical trials at this point.

More information: UV damage-induced RNA polymerase II stalling stimulates H2B deubiquitylation, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1403901111

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