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Study reveals new insight into DNA repair

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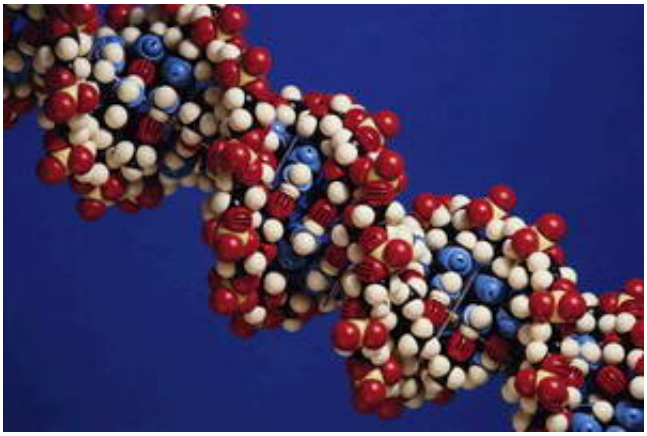

DNA double-strand breaks (DSBs) are the worst possible form of genetic malfunction that can cause cancer and resistance to therapy. New information published this week reveals more about why this occurs and how these breaks can be repaired.

Scientists at The University of Texas MD Anderson Cancer Center reported their findings about the role of the enzyme fumarase in DNA repair in the Aug. 3, 2015 issue of *Nature Cell Biology*.

"Our study showed that the enzymatic activity of the metabolic enzyme fumarase and its product, fumarate, are critical elements of the DNA damage response and that fumarase deficiency promotes tumor growth due to impairment of DNA repair," said Zhimin Lu, M.D., Ph.D.,

professor of Neuro-Oncology.

Lu's team demonstrated that fumarase accomplishes this through a process critical for gene regulation and expression known as histone methylation. Many cancers are thought to result from misregulated histone methylation.

Another crucial component of the DNA repair process is DNA-PK, a protein kinase that governs DNA damage response, helping to assure genetic stability. The researchers defined how DNA-PK and fumarase interact to increase histone methylation, allowing for DNA repair and restoration of healthy cells.

"We know that histone methylation regulates DNA repair, but the mechanisms underlying this repair has not been fully understood," he said. "Our research revealed a 'feedback' mechanism that underlies DNA-PK regulation by chromatin-associated fumarase and the function of this fumarase in regulating histone methylation and DNA repair."

This chain-of-event repair process occurs at the DSB regions and initiates a DNA damage "fix" by joining the tail ends of the double strand breaks.

Increasingly, inhibition of DNA-PKs and fumarase are being looked at for its potential to sensitize cancer cells to chemotherapy or radiotherapy. It is hoped a more thorough understanding about how they accomplish this can lead to new approaches to cancer treatment.

Dr. Lu's group previously reported that another metabolic enzyme, pyruvate kinase M2 (PKM2) acts as a protein kinase in regulation of the Warburg effect, a process by which cancer cells produce energy, as well for regulation of gene expression and cell cycle progression.

"Our new findings on fumarase's role in DNA repair further demonstrate that metabolic enzymes can possess non-metabolic functions in crucial cellular activities of cancer cells," said Lu.

More information: *Nature Cell Biology*. DOI: 10.1038/ncb3209

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