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Researchers pinpoint how one cancer gene functions

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For several decades, researchers have been linking genetic mutations to diseases ranging from cancer to developmental abnormalities. What hasn't been clear, however, is how the body's genome sustains such destructive glitches in the first place. Now a team of Mayo Clinic scientists and collaborators provide an unprecedented glimpse of a little-understood gene, called MMSET, revealing how it enables disease-causing mutations to occur. The findings appear in the current issue of *Nature*.

"MMSET had been known for many years, and had been shown to be mutated in several diseases, but its function had never quite been pinpointed," says lead author Zhenkun Lou, Ph.D., Mayo Clinic pharmacologist and senior author of the study.

The researchers found that normally-functioning MMSET is usually helpful. It plays a restorative role within the genome, recruiting proteins like p53-binding protein 1 to repair breaks that occur in DNA and to maintain genetic stability. But when MMSET malfunctions, the protective pathway falls short, and a cascade of mutations take place that can lead to disease processes.

"It was not clear before the study how p53-binding protein 1 was targeted to sites of DNA damage. We found MMSET regulates this critical pathway," Dr. Lou says. "But when the gene is impaired, cells don't have the correct response to DNA damage." Misregulation of MMSET has been implicated in cancers like the plasma cell cancer

multiple myeloma as well as the inherited disorder of severe retardation known as Wolf-Hirschhorn syndrome, even though the MMSET mutation looks different in the two diseases.

While the study answers a long baffling mystery about the function of the gene, it also suggests avenues for new therapeutic approaches for several disorders, notes Dr. Lou. One possible route for clinical investigation is for patients with MMSET mutations, which keep DNA from undergoing efficient repair, to be given treatment that will help minimize genetic damage. For instance, patients with defects in DNA damage-maintenance machinery often succumb to neurological disorders (e.g., ataxia telangiectasia and Wolf-Hirschhorn syndrome), since neurons are very sensitive to DNA damage spontaneously occurring in cells. These patients could be given anti-oxidative treatment to help maintain the health of DNA and preserve neurons.

The finding also suggests new thinking about treating certain cancers. MMSET protein has been found in abundance in hard-to-treat malignancies such as multiple myeloma and glioblastoma, a devastating brain tumor.

"It may be that these cancers don't respond well to chemotherapy treatment, which works by interrupting DNA, because the [MMSET producing] cancer cells are more efficient at repairing themselves," Dr. Lou says. Dr. Lou is currently working with the National Institutes of Health-Mayo Brain Tumor SPORE (Specialized Program of Research Excellence) to investigate whether MMSET levels will be a biomarker to guide glioblastoma treatment. Future investigations may involve inhibiting MMSET in proliferating cancer cells, which may make cancers more responsive to cell-killing chemotherapies.

Provided by Mayo Clinic