# Wip1 could be new target for cancer treatment

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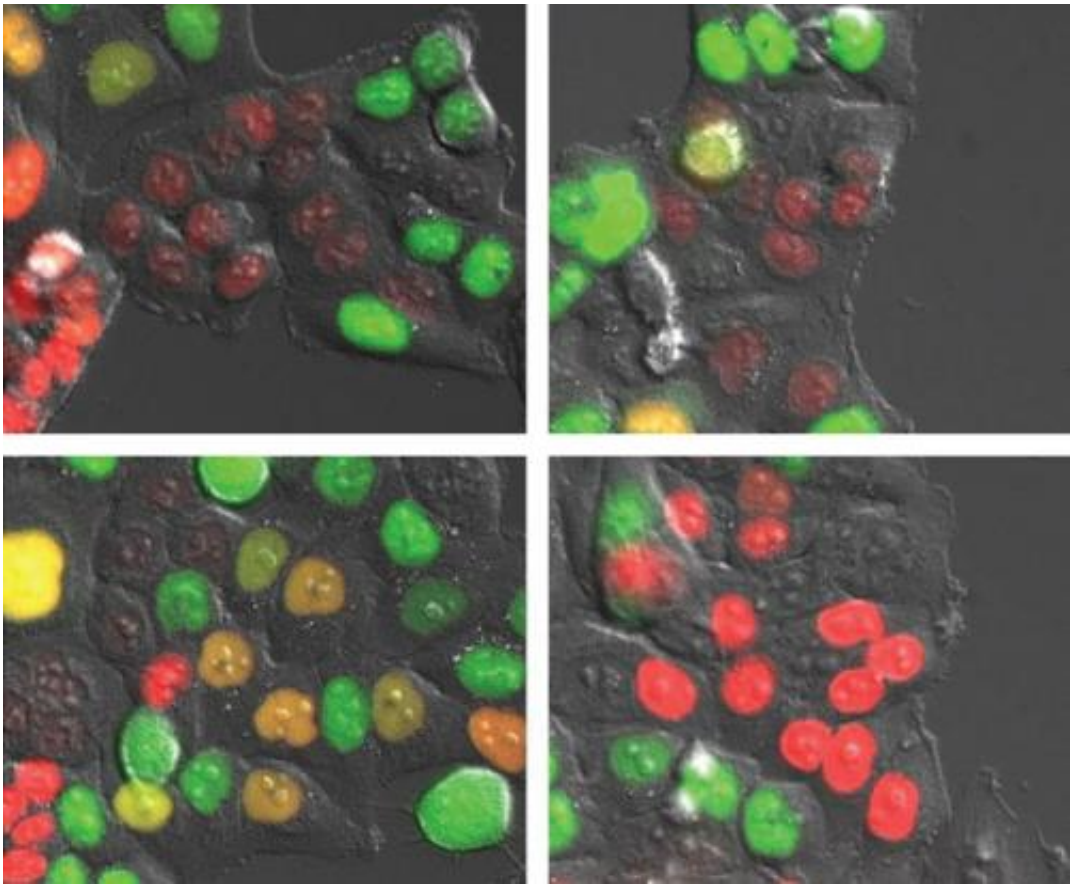

Researchers tracked down mutations in the phosphatase Wip1 in cancer cells that enhance the protein's ability to shut down p53 and stymie the DNA damage repair process. The panel shows how cells respond to a dose of radiation that normally stops cells from dividing. The top row shows the cells one hour after the radiation, and the bottom row shows them 17 hours afterward. Cells with truncated Wip1 (left column) progress normally toward the point of cell division (orange nuclei), but most cells lacking truncated Wip1 (right column) fail to progress (red nuclei). Credit: Indra Shaltiel

Researchers have uncovered mutations in the phosphatase Wip1 that enable cancer cells to foil the tumor suppressor p53, according to a study in *The Journal of Cell Biology*. The results could provide a new target for the treatment of certain cancers.

Like a battlefield surgeon who has to decide which casualties can be saved, p53 performs triage on cells with injured DNA. If the damage is serious, p53 spurs the cells to die or stop proliferating. But after milder hits, p53 activates a DNA damage response (DDR) mechanism, which instigates repairs, and temporarily prevent cells from advancing any farther in the cell cycle. Once cells have mended their DNA, the phosphatase Wip1 enables them to re-enter the cell cycle by shutting down p53 and DDR proteins. Because p53 and the DDR stymie cancer cells, it's no surprise that the rogue cells find ways to circumvent this protection. More than half of all cancers accrue mutations in the p53 gene, for example. Now, researchers from the Czech Republic and the Netherlands tested whether some cells instead carry mutations in the *PPM1D* gene, which encodes Wip1, to shut down p53.

The team analyzed human tumor cell lines that harbor functional p53. Two of the lines displayed mutations in exon 6 of the *PPM1D* gene that resulted in a shortened version of Wip1. The truncated Wip1 was more stable than the full-length version of the protein, allowing cells to switch off p53 and continue the cell cycle in the presence of DNA damage. Depleting the truncated Wip1, however, halted the cell cycle until the DNA was repaired.

The researchers then looked for *PPM1D* mutations in 1,000 patients who had colorectal or breast and ovarian cancer. Four of the patients carried mutations, whereas none of the 450 cancer-free individuals did. All of these DNA alterations fell in exon 6 and caused production of shortened

Wip1. To the researchers' surprise, the mutations occurred in the cancer patients' non-tumor cells as well. That suggests that the patients were born with *PPM1D* mutations, which set them up for cancer later in life but apparently caused no other illnesses.

"We've identified a new mechanism that could lead to inactivation of p53 in cells and inactivation of the DNA damage response," says senior author Libor Macurek. The team suspects that *PPM1D* mutations could turn up in a variety of tumors. If so, targeting the short but overactive form of Wip1 could provide a new way to treat these cancers.

**More information:** Kleiblova, P., et al. 2013. J. Cell Biol. doi:10.1083/jcb.201210031

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