Researchers discover key protein involved in DNA repair

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In a groundbreaking study, University of Toronto researchers including Professors Daniel Durocher, Anne-Claude Gingras and Frank Sicheri have uncovered a protein called OTUB1 that blocks DNA damage in the cell -- a discovery that may lead to the development of strategies to improve some cancer therapies.

Lead author Durocher, a senior investigator at Mount Sinai Hospital's Samuel Lunenfeld Research Institute and the Thomas Kierans Research Chair in Mechanisms of Cancer Development, as well as colleagues at U of T, Mount Sinai Hospital and the Keio University in Japan, have revealed pivotal new information on how cells regulate their genetic material. In addition, the discovery improves understanding of familial breast and ovarian cancer, as the research shows that OTUB1 inhibits the action of BRCA1, a DNA repair protein often mutated in these cancers.

"In recent years, we have been very good at finding proteins necessary for DNA repair," said Durocher. "What we did not appreciate was that gatekeepers existed to inhibit the capacity of the cell to repair DNA. The obvious question now is: Can we enhance the ability of the cell to repair DNA by blocking OTUB1?"

The findings were reported in the August 19 issue of the prestigious international journal *Nature*, in which only one or two highâ€impact papers are published weekly. The researchers identified OTUB1 using RNA interference (or RNAi), an approach that helps scientists determine the functions of proteins and genes. After exposing cells to

radiation, Durocher and his team used RNAi to discover that OTUB1 inhibits a cell's DNA repair mechanisms, through its role in a process known as ubiquination.

Ubiquitins are small regulatory proteins in cells. The addition of many ubiquitins onto a target
protein can act as a 'mayday' signal at the site of DNA damage, attracting repair mechanisms to fix the damage. Durocher's team found that OTUB1 mutes the mayday signal by preventing the addition of ubiquitin units.

"Perhaps the biggest surprise was that OTUB1 works by an entirely new and elegant mechanism," said Durocher. "Mutations in genes that repair our DNA can lead to cancer, infertility and immune deficiency. Therefore, inhibiting the proteins that block DNA repair could lead to new types of therapeutics for these diseases."

For example, Durocher explained that by inhibiting OTUB1, healthy cells may be better able to withstand cancer treatment with radiation and certain chemotherapy medications such as doxorubicin. As well, inhibiting OTUB1 may lead to treatments for genetic immunodeficiency disorders such as RIDDLE syndrome, in which cells lose their ability to repair DNA damage.

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