Graduate student finds a 'start/stop switch' for retroviruses

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A University of British Columbia doctoral candidate has discovered a previously unknown mechanism for silencing retroviruses, segments of genetic material that can lead to fatal mutations in a cell's DNA.

The findings, published today in the journal *Nature*, could lead to new cancer treatments that kill only tumour cells and leave healthy surrounding tissue unharmed.

Danny Leung, a 27-year-old graduate student in the laboratory of Asst. Prof. Matthew Lorincz in the Dept. of Medical Genetics, UBC Faculty of Medicine, found that a protein called ESET is crucial to preventing the activity of endogenous retroviruses in mouse embryonic stem cells. Distant relatives of such retroviruses are more active in the cells of testicular, breast and skin cancers in humans.

If ESET can be blocked, retroviruses would become dramatically more active, thus either killing the cancer cells hosting them or flagging them as targets for the immune system.

Leung, who was co-lead author with a graduate student at Kyoto University in Japan, has devoted his studies at UBC to the growing field of epigenetics - changes to the genome that do not involve changes to the underlying genetic code. Such changes determine whether or not a gene is expressed.

The common method for silencing certain genes is DNA methylation, in

which a chemical group attaches to the DNA structure. But Leung and his collaborators at UBC and Kyoto University found that the activity of ESET is far more potent than DNA methylation in silencing retroviruses in embryonic stem cells of mice. This indicates an independent parallel pathway of silencing the retroviruses.

Their research has direct bearing on cancer treatments because cancer cells are stem-like - they can differentiate into other types of cells. Also, for unknown reasons, cancer cells have significantly less DNA methylation than normal cells. So blocking ESET holds the promise of affecting only cancer cells, allowing retroviruses to flourish to the detriment of their hosts. Normal, differentiated cells, which still have DNA methylation to keep retroviruses in check, would be unaffected.

"Inhibiting ESET may affect just the cancer cells, allowing further expression of retroviruses, which in turn would kill the cancer cells," says Leung, who is in his third year of graduate studies at UBC. His co-lead author on the paper, Toshiyuki Matsui, is a student in the lab of Yoichi Shinkai at Kyoto University.

Provided by University of British Columbia