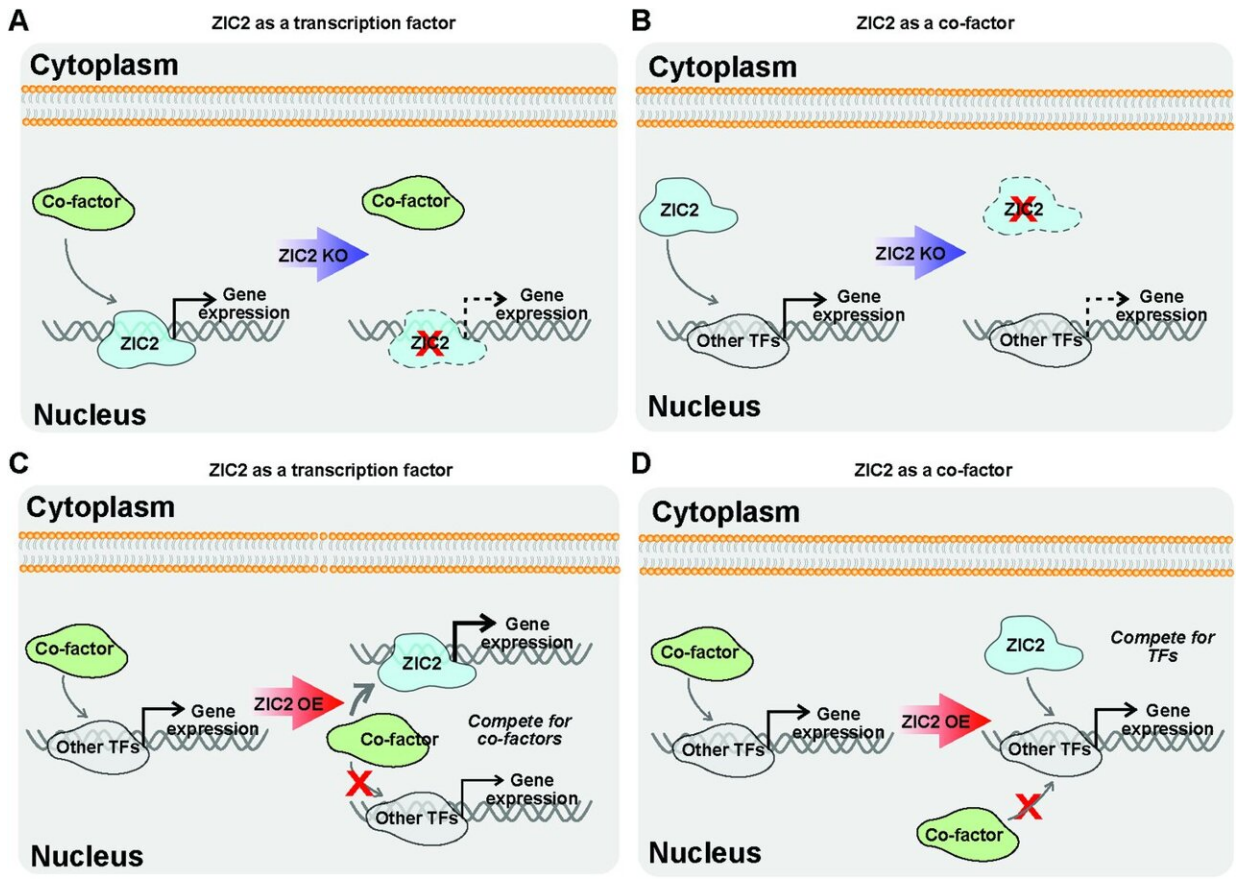
Gene found in ovarian cancer cells identified as potential new target for treatment

September 3 2024, by Gillian Rutherford



A potential model for ZIC2 functions in EOC. Credit: *Oncogene* (2024). DOI: 10.1038/s41388-024-03026-z

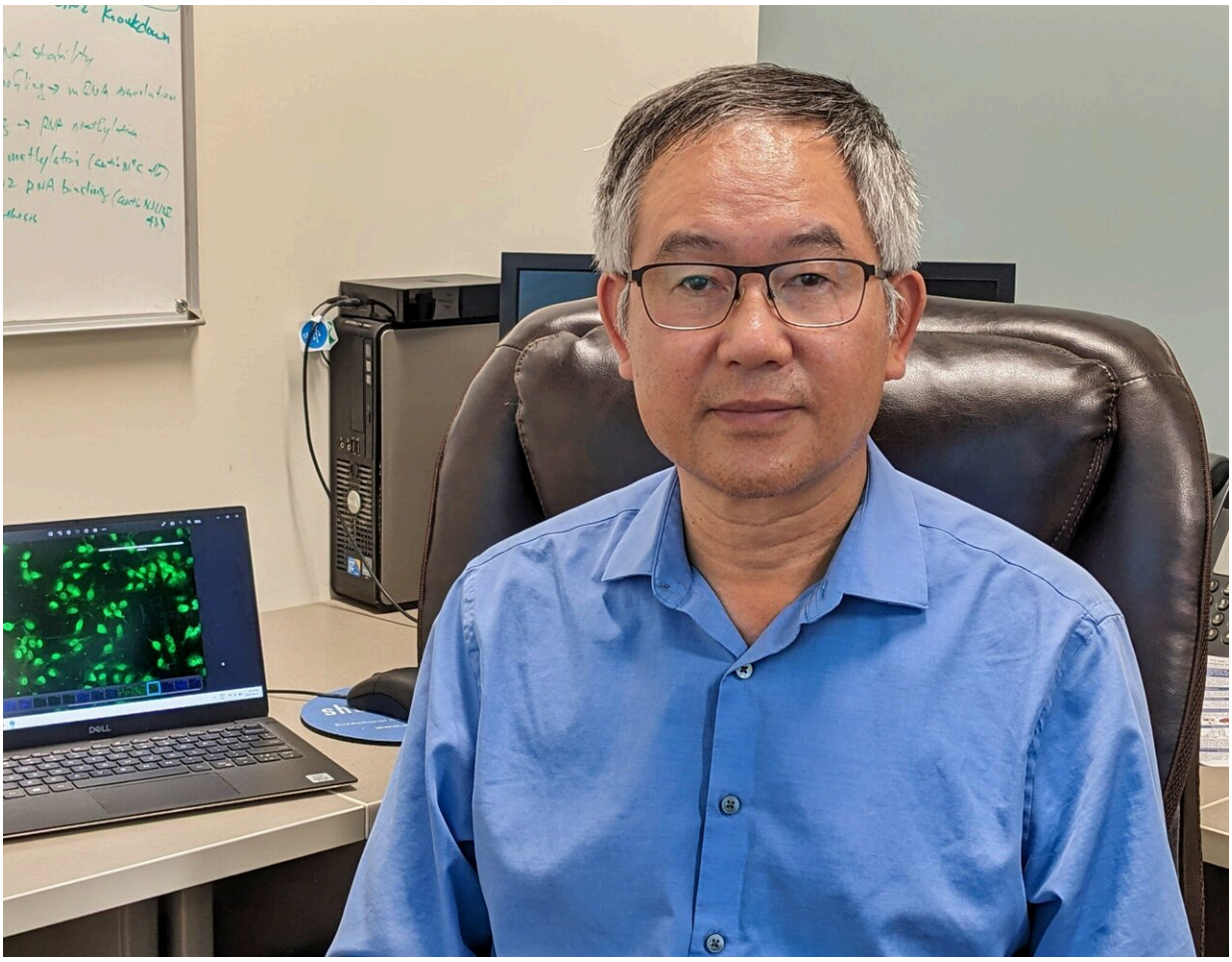
A University of Alberta research team has found a potential new

treatment target for ovarian cancer. Their new research is the first to comprehensively investigate the elevated expression of a gene called ZIC2 in ovarian cancer cells, finding that it is associated with poor survival rates of ovarian cancer patients and testing ways to inactivate the gene.

The research is published in the journal *Oncogene*.

Ovarian cancer is predicted to kill an estimated 2,000 women in Canada this year, according to the Canadian Cancer Society. About a quarter of ovarian cancer cases show elevated levels of ZIC2 protein in the cancer cells.

ZIC2 protein is produced by the ZIC2 gene, which normally is responsible for human brain development in the embryonic stage and then remains inactive in adults except in the brain and testis. It is not understood why the gene gets reactivated in ovarian cancer with such deadly results.



YangXin Fu. Credit: University of Alberta

"Currently, there's no effective treatment for ovarian cancer," says YangXin Fu, associate professor of experimental oncology and adjunct associate professor of obstetrics and gynecology. "Also, ovarian cancer cases are often diagnosed at a late stage and by that time, even with surgery and chemotherapy, the cancer recurs and becomes resistant to chemotherapy.

"That is why we need to find a new treatment."

The team started by testing for ZIC2 in test tubes, using human cell lines of ovarian cancer. They identified those that exhibited high expression of the gene and then used CRISPR technology to inactivate it. They found cancer cells with inactivated ZIC2 grew more slowly, migrated less and formed fewer and smaller colonies.

They then repeated the experiments by implanting the ovarian cancer cells in mice and observing their behavior. Again, they found a similar slowing of cancer development in tumors where the ZIC2 gene had been inactivated.

"When we inactivate ZIC2 in those cancer cells, they become less aggressive and form smaller tumors in mice," says Fu. "Of course, it's a huge step to go from animal work to a clinical trial in humans, but it shows that in the future, if we can find a way to inhibit ZIC2 function, it might reduce tumor formation and progression and provide an effective treatment."

ZIC2 is a transcription factor, which means it has the ability to turn many other genes on or off, a kind of "master regulator," explains Fu, but it is rarely expressed in adults except in ovarian cancer tissue, so he believes it is safe to target.

Interestingly, the team tried adding ZIC2 to ovarian cancer cell lines that did not express it naturally and found to their surprise that it did not increase tumor growth. This indicates the ZIC2 treatment is context-specific, says Fu, meaning that it would have to be specific to cells where the gene is already present.

Fu says the next step for the research will be to search for ways to inactivate ZIC2 in human patients, since CRISPR is not yet used for human treatment.

He says the team will hunt for small-molecule drugs that can inhibit the function of the gene and will also explore the proteolysis targeting chimera or PROTAC approach, which is capable of removing specific unwanted proteins.

More information: Huachen Chen et al, Transcription factor ZIC2 regulates the tumorigenic phenotypes associated with both bulk and cancer stem cells in epithelial ovarian cancer, *Oncogene* (2024). DOI: 10.1038/s41388-024-03026-z

Provided by University of Alberta