

Investigation of the role of the *WWOX* gene as a suppressor of ovarian tumorigenesis

Researchers

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Aim

An ovarian cancer cell line developed in Edinburgh (PEO1) was found to have lost both copies of a gene called *WWOX*. When this gene was put back into these cancer cells they could no longer form tumours. The aims of this project were to:

- 1) Establish why loss of *WWOX* helps ovarian cancer grow.
- 2) Determine whether loss of *WWOX* helps ovarian cancer cells survive as they spread from their primary site to secondary sites in the abdomen and pelvis.
- 3) Identify other genes and proteins that interact with *WWOX* and help the survival of ovarian cancer cells in a way that could be targeted with new therapies.

Project Outline/Methodology

Different types of ovarian cancer cells were grown in culture. Levels of *WWOX* were either increased (by adding extra copies of the gene) or decreased (by using a molecule called siRNA). The effects of manipulating the *WWOX* levels in the cancer cells were then monitored in experiments assessing their ability to survive and to adhere to their surroundings. The cells were then used to identify proteins important in cancer, that were affected by *WWOX* in the hope that these may be targets for therapy in the future.

Key Results

- 1) In 3 different ovarian cancer cell lines it was shown that higher *WWOX* levels made the cells less able to adhere to fibronectin, a molecule that helps them survive in the body.
- 2) *WWOX* causes a reduction in the level of molecules called integrins at the cell surface. Integrins help the cell attach to fibronectin.
- 3) Replacement of *WWOX* in ovarian cancer cells makes them less able to survive when grown in suspension (circumstances which mimic ovarian cancer cells as they spread in the body).
- 4) A pathway of proteins was identified that respond normally to cellular adhesion in cells containing *WWOX* but not in cells lacking the gene.

5) One of these proteins is a possible binding partner for the *WWOX* protein and this protein only reacts to cellular adhesion in the presence of *WWOX*. This protein may represent a new drug target in ovarian cancer.

Conclusions

WWOX plays a role in decreasing the attachment of cells to surrounding tissues and in preventing their survival when unattached (this prevents cancer). When *WWOX* is absent there is dysregulation of a pathway usual activated by cellular adherence. This pathway could be targeted for therapeutic benefit.

What does this study add to the field?

This is the first demonstration that *WWOX* can affect integrin levels and the attachment of cancer cells to surrounding tissues. Integrins are crucial not only for binding to surrounding tissues but also for providing signals to the cell to enable it to survive. This is borne out when we show that *WWOX* facilitates cell death in cells grown in suspension. These findings emphasise the importance of the *WWOX* pathway in ovarian cancer cell survival and suggest that manipulation of the pathway is a therapeutic avenue that should be explored. With this in mind we have identified proteins that may be important in this pathway and could represent future drug targets.

Implications for Practice or Policy

The molecules involved in the processes described above represent potential drug targets. Some (such as integrins) are already being investigated but others are not. The latter require to be validated then inhibitors developed and tested for efficacy.

Where to next?

We need to verify the importance of the proteins identified above in further cell line systems and in human ovarian cancer samples and demonstrate that interruption of these pathways would be beneficial in the treatment of ovarian cancer.

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