Scottish Government Health Directorates Chief Scientist Office

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Characterisation of the role of *ERCC1* induction following platinum-based chemotherapy in ovarian cancer resistance in vivo and investigation of therapeutic strategies to inhibit this process

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Aim
To determine whether *ERCC1* gene expression or induction following platinum therapy predicts platinum resistance in ovarian cancer. Also, to establish the role of the mitogen activated protein kinase pathway in the mechanism of resistance.

Project Outline/Methodology
We used ovarian cancer cell lines including matched lines derived from patients before and after the development of resistance to platinum chemotherapy to determine the role of *ERCC1* and the mitogen activated protein kinase pathway in the development of platinum resistance. Gene expression was assessed by Western blot and Taqman assay.
We previously described three main subgroups of high grade serous ovarian cancer characterised by high expression of angiogenesis genes (subgroup named Angio), immune response genes (subgroup named Immune) and both angiogenesis and immune response genes (subgroup named Angioimmune). Immune subgroup patients have superior survival to patients in the Angio and Angioimmune subgroups. In the current project we applied gene signatures to identify these molecular subgroups to matched paired tumours obtained from patients at diagnosis and following chemotherapy and relapse in order to determine whether molecular subgroups switch and to investigate the predominant biology at relapse.

Key Results
We demonstrated no association between *ERCC1* gene expression or induction following chemotherapy and platinum resistant ovarian cancer.
Gene expression analysis in the matched paired patient specimens revealed that patients in both the good prognosis Immune subgroup and the Angio subgroup frequently switched to the Angioimmune subgroup at relapse. In particular subgroup switching from Immune to Angioimmune was significantly associated with the development of platinum resistance. Patients who remained in the Immune subgroup were more likely to remain platinum sensitive. Only 1/35 (3%) patients switched from a poor prognosis subgroup into the good prognosis Immune subgroup.
We subsequently demonstrated that the Angioimmune subgroup is characterised by activation of the mitogen activated protein kinase pathway and that these tumours are sensitive to the MEK inhibitor trametinib.

Conclusions
Relapse of high grade serous ovarian cancer is associated with clonal selection of cells that are platinum resistant, driven by the mitogen activated protein kinase pathway and that can be identified using a gene signature.

What does this study add to the field?
This study identifies a novel mechanism of platinum resistance in high grade serous ovarian cancer. It also defines a gene signature that can be used to identify patients whose tumours exhibit this biology, providing an opportunity for stratified clinical trials.

Implications for Practice or Policy
The fact that these cells are targetable using MEK inhibitors raises the possibility of performing clinical trials either in the resistant disease setting or even prior to the development of resistance in order to kill these cells before they proliferate. Gene expression analysis can be used to identify the patients most likely to benefit from this strategy.

Where to next?
We plan to assess whether the molecular subgroup switching seen in this study is replicated before and after neoadjuvant chemotherapy and if so whether this predicts response to or outcome following neoadjuvant chemotherapy. Thereafter our aim would be to propose clinical trials targetting these cells in order to improve patient outcome.

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