BGCS 2017
British Gynaecological Cancer Society
Annual Scientific Meeting
15th -16th June 2017 - Technology and Innovation Centre, Glasgow
In Collaboration with: NCRI National Cancer Research Institute

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INHIBITION OF MATERNAL EMBRYONIC LEUCINE-ZIPPER KINASE IS A NOVEL THERAPY FOR NON-UTERINE PELVIC HIGH GRADE SEROUS CARCINOMA.

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Introduction

Non-uterine pelvic high grade serous carcinoma (HGSC) is the most common, most aggressive, subtype of epithelial ovarian cancer. It carries a poor prognosis due to its typically late presentation. The underlying molecular profile of HGSC has been shown to be driven by dysregulated mitotic activity. A key driver of this being Maternal Embryonic Leucine-Zipper Kinase (MELK).

Methods

Six cases of HGSC were identified through the Northern Ireland Gynaecological Cancer Centre. All were FIGO stage IIIC+ carcinomas with matched clinicopathological data. Gene expression profiling (GEP) (Almac Xcel®) was performed on the following formalin-fixed paraffin embedded (FFPE) tissue samples from each case: Normal FT, STIC, HGSC, and Omental metastases. The GEP results were independently validated using RqPCR. Bioinformatic analysis of the data revealed dysregulated mitotic activity to be a driver of malignant transformation from normal FT to STIC.

A siRNA screening assay was designed to assess the potential of MELK as a key regulator of the mitotic activity. This was analysed by RqPCR, western blotting and cell viability assays. Subsequently, a novel MELK-inhibitor, OTSSP167, was analysed, using drug-screening assays, on a HGSC-specific cell model in comparison with platinum-taxol “standard-of-care”.

Results

The inhibition of MELK by siRNA has a significant impact on HGSC cell viability and there is evidence of downstream inhibition of a number of key mitotic genes (identified from the GEP dataset). The novel MELK-inhibitor has a significantly greater chemotherapeutic activity on the HGSC cell model compared to standard of care.

Conclusions

MELK overexpression in HGSC is likely to be a key driver of malignant transformation. Inhibiting this pathway with OTSSP167 is a potential therapeutic strategy for patients suffering from HGSC.