PPP2R1A mutations cause ATR inhibitor sensitivity in ovarian clear cell carcinoma

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Presenter: Chen-Wei Su **Date/Time**: 2025/12/11, 16:20-17:10

Commentator: Dr. Chi-Wu Chiang **Location**: Room 601, Med College Building

Background

Ovarian clear cell carcinoma (OCCC) is a type of epithelial ovarian cancer and notoriously resistant to conventional cytotoxic chemotherapy, leading to poor outcomes in advanced disease stages. Truncating mutations in the SWI/SNF tumor suppressor ARID1A are most found genetic alterations in OCCC, and were identified to cause synthetic lethality with ATR inhibition (ATRi), which have motivated ongoing ATR inhibitor AZD6738 clinical trials on advanced gynaecological cancers. In addition to ARID1A alterations, it was not known whether there are any other genes involved in modifying ARID1A/ATRi synthetic lethality.

Objective

The authors aimed to identify genetic modifiers of ARID1A/ATRi synthetic lethality.

Results

Genome-wide CRISPR mutagenesis and interference screens identified several genes modifying sensitivity to ATRi in the presence of ARID1A mutations. Among these genes, loss of several PP2A subunits, including PPP2R1A, enhanced sensitivity to ATR inhibition (ATRi). Analysis of a OCCC patient cohort, 52% of patients' tumors carried oncogenic PPP2R1A p.R183 mutations, 33% of these co-occurring with ARID1A loss. Using CRISPR-prime editing to generate new isogenic models in ARID1A mutant OCCC cells, the heterozygous PPP2R1A p.R183 mutations were found to cause increased sensitivity to ATRi *in vitro*. These mutations cause ATRi-induced S phase stress, premature mitotic entry and genomic instability. *In vivo* orthotopic xenograft tumor model, low dose of ATRi suppressed OCCC tumor growth in the presence of the PPP2R1A mutation.

Conclusion

Oncogenic PPP2R1A p.R183 hotspot mutations enhance the sensitivity of OCCC preclinical models to ATR inhibitors (ATRi). These findings indicate that PPP2R1A status is an important modifier of ATRi response. Therefore, the results support evaluating PPP2R1A mutations as a key biomarker for ATRi sensitivity and incorporating PPP2R1A testing into ongoing or future clinical trials.