Medical & healthcare, Drug discovery, Ovarian cancer

Identification of the ovarian cancer cell subpopulation that contributes to therapeutic agents resistance

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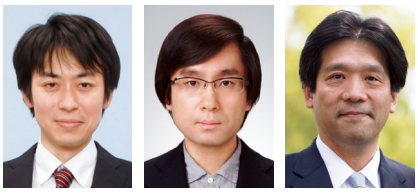

Abstract

Platinum resistance is a major obstacle to the treatment of ovarian cancer and is correlated with poor clinical outcomes. Although there have been many studies of platinum resistance in ovarian cancer, the underlying molecular mechanisms have not been fully elucidated. We showed that low expression of SMARCA4 and high expression of SMARCA2 were associated with platinum resistance in ovarian high-grade serous carcinoma (HGSC) cells. We used fluorescence multiplex immunohistochemistry to study resected specimens; we examined heterogeneity in human HGSC tissues at the single-cell level, which revealed that the proportion of cells with the SMARCA4^{low}/SMARCA2^{high} phenotype was positively correlated with clinical platinum-resistant recurrence. We used stable transfection of SMARCA2 and siRNA knockdown of SMARCA4 to generate HGSC cells with the SMARCA4^{low}/SMARCA2^{high} phenotype; these cells had the greatest resistance to carboplatin. Bioinformatics analyses revealed that the underlying mechanism involved in substantial alterations to chromatin accessibility and resultant fibroblast growth factor (FGF) signaling activation. Furthermore, *in vivo* experiments in an animal model demonstrated that combination therapy with carboplatin and a fibroblast growth factor receptor (FGFR) inhibitor promoted cell death in HGSC xenografts.

Background & Results

Platinum-based chemotherapy is an essential treatment for patients because HGSC is often detected at an advanced stage and relapses are frequent. Therefore, the discovery of novel biomarkers and classification systems to predict responsiveness to HGSC therapy has remained a challenge for gynecological oncology.

This study demonstrated that evaluation of the proportion of cells with the SMARCA4^{low}/SMARCA2^{high} phenotype in HGSC specimens can help to predict platinum-resistant recurrence, which may lead to the establishment of novel histopathological diagnostic systems.

Single-cell imaging analysis of SMARCA4/A2 expression patterns in HGSC tissues revealed that SMARCA4^{low}/SMARCA2^{high} subpopulation is presumably responsible for platinum resistance and recurrence in HGSC patients. *In vitro* functional experiments showed that the HGSC cell line with SMARCA4^{low}/SMARCA2^{high} phenotype exhibited the greatest resistance to carboplatin in the chemoresistance assay. Bioinformatics analyses revealed that the underlying mechanism of platinum resistance in SMARCA4^{low}/SMARCA2^{high} HGSC cells involved substantial alterations to chromatin accessibility and resultant fibroblast growth factor (FGF) signaling activation, MAPK pathway activation, BCL2 overexpression, and reduced carboplatin-induced apoptosis. Furthermore, *in vivo* experiments in an animal model demonstrated that combination therapy with carboplatin and a fibroblast growth factor receptor (FGFR) inhibitor promoted cell death in HGSC xenografts.

Significance of the research and Future perspective

We discovered an association between the SMARCA4^{low}/SMARCA2^{high} phenotype and chemoresistance in HGSC, and we characterized a mechanism that underlies the FGFR1–pERK1/2–BCL2 axis. Our findings may lead to the establishment of a novel system for predicting the chemotherapy response and of a new therapeutic strategy for patients with platinum-resistant recurrence.

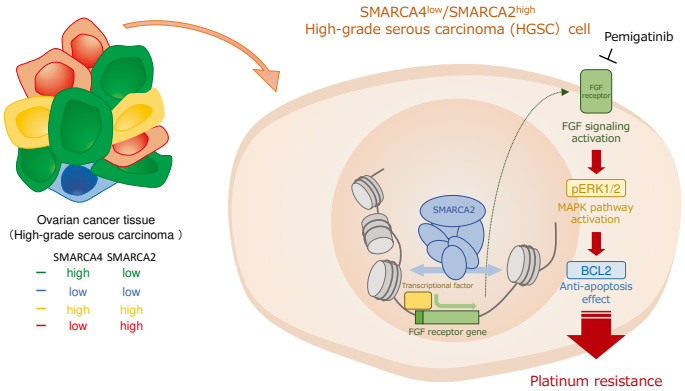

Figure 1. Schematic of the mechanisms by which SMARCA4^{low}/SMARCA2^{high} high-grade serous carcinoma cells contribute to platinum resistance.

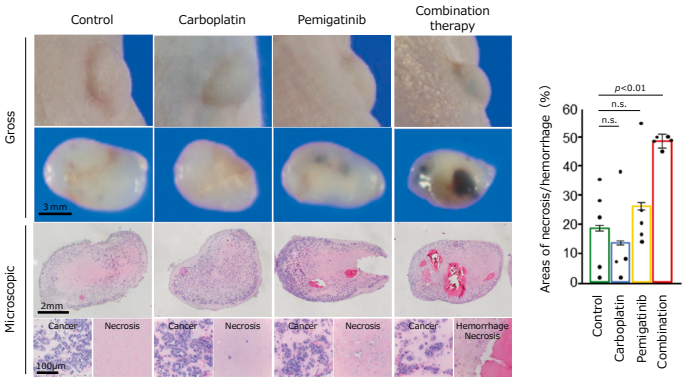

Figure 2. Inhibition of high-grade serous carcinoma xenograft proliferation by *in vivo* treatment with carboplatin and an FGF receptor inhibitor. (Left) Representative gross and H&E-stained images of the xenografts. (Right) A bar chart showing proportions of areas of necrosis/ hemorrhage.

Patent

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