

DCLK1 Promotes Cisplatin Resistance in Ovarian Cancer

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Introduction: High grade serous ovarian carcinoma (HGSOC) is the most common and lethal histologic subtype of ovarian cancer (OvCa) that accounts for 80% of OvCa deaths. Poor survival is attributed to disease recurrence and drug resistance to platinum-taxol-based drugs, which are the first-line treatment. Thus, developing effective treatments that overcome resistance to standard-of-care treatments are urgently needed. Doublecortin-like kinase 1 (DCLK1) is a microtubule-associated protein family member known to regulate microtubule turnover and distribution. It is a major regulator of cancer cell “stemness”, epithelial-mesenchymal transition (EMT), and promotes tumor progression, and metastasis. The study objective is to assess the functional role of DCLK1 in mediating platinum-resistance in OvCa and associated benefits from antagonizing this pathway as a novel treatment strategy to prevent OvCa recurrence.

Methods: DCLK1 expression was evaluated under adherent (2D) and suspended spheroid (3D) conditions in a panel of human OvCa cell lines representative of HGSOC, and platinum-sensitive and resistant cell lines using western blot. Pharmacological inhibition (DCLK1-IN-1) and genetic manipulation (DCLK1 CRISPR knockout) were used to assess the role of DCLK1 in mediating cisplatin resistance. Drug sensitivity assays were performed using live-cell imaging analysis (Incucyte) and 3D cell viability assays. Migration and invasion of human OvCa cells was determined *in vitro* in the presence of DCLK1-IN-1. Western blots were performed to evaluate the effect of DCLK1 inhibition on markers for EMT, OvCa cell stemness, and a potential kinase substrate. Differential expression of microRNAs critical for mediating drug resistance and EMT were measured by RT-PCR in DCLK1 deficient cells.

Results: DCLK1 is differentially expressed in a panel of human OvCa cell lines representative of HGSOC when cultured under both 2D and 3D conditions. We also observed significant DCLK1 upregulation in cisplatin-resistant OvCa cell lines relative to their sensitive controls (OVCAR-8 and IGROV-1). Inhibition of DCLK1 was effective in restoring cisplatin sensitivity and reducing pro-tumorigenic phenotypes (e.g., cell migration & invasion) in platinum-resistant OvCa cells. We observed that DCLK1 knockout differentially affected markers for cancer cell stemness and microRNA expression.

Conclusions: Our study showed that DCLK1 is important in regulating programs promoting platinum resistance in OvCa. Use of DCLK1 specific inhibitors will provide a rationale and optimal therapeutic strategy to overcome cisplatin resistance in a clinical setting.