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Abstract 70: A role for the chromatin remodeling protein CHD3 in ovarian cancer therapy response

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Abstract

Carboplatin and cisplatin are chemotherapeutic agents that are used extensively for treating epithelial ovarian cancer. These drugs can be highly effective, yet tumors are frequently refractory to treatment or become resistant upon tumor relapse. Epigenetic silencing, particularly at promoter regions of genes regulates important cell function and has been associated with all stages of tumor formation and progression and may contribute to therapy response. We analyzed the epigenome of 50 primary ovarian tumors and 12 normal ovarian samples using an array based method previously developed in our lab and associated Affymetrix U133 expression data. We then identified gene candidates that segregate patients based on platinum sensitivity and patient survival. These candidates were then pooled into a genome-wide RNAi-based screen where we validated a gene encoding a chromatin remodeling protein, CHD3, a member of the Mi-2 NuRD complex, and show that it is linked to chemoresistance. CHD3 is silenced through an epigenetic mechanism in both ovarian cancer cell lines and primary ovarian tumors. When ovarian cancer cell lines that are transcriptionally silenced for CHD3 are challenged with carboplatin they display a striking slow growth phenotype as well as increased resistance to the chemotherapy drugs carboplatin and cisplatin. Taken together, we provide the first evidence for a role for CHD3 as an important mediator of chemoresistance in ovarian cancer. Furthermore, CHD3 might represent a response predictor and potential therapeutic target for predicting chemoresistance in this disease.