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## Abstract 3144: A role for DOK2 methylation in platinum resistance and tumor suppression in ovarian cancer

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## Abstract

Ovarian cancer is the 5th leading cause of cancer in women, affecting close to 22,000 women in the year 2011, of which nearly 15,500 will die. It is difficult to detect until it reaches advanced stages and becomes malignant. Currently, the standard treatment for ovarian cancer is platinum-based therapeutics, such as Carboplatin or Cisplatin, combined with Taxol. Unfortunately, approximately 25% of patients are inherently platinum-resistant and all patients who suffer from recurrence will have developed acquired platinum resistance. The genetic/epigenetic causes of this resistance are poorly understood. Epigenetic events are reversible and the identification of genes altered by this mechanism may lead to studies on how to reprogram the process leading up to resistance. To examine the ovarian epigenome, we utilized an array based method, Methylation Oligonucleotide Microarray Analysis (MOMA), to analyze a set of 50 primary ovarian tumors and 12 ovarian normal samples. We identified epigenetic differences that segregated with platinum response and then associated this with expression data to identify gene candidates transcriptionally repressed and methylated in patients resistant to platinum. Next, a pooled shRNA screen was performed on candidate genes to identify those that were functionally relevant to platinum resistance. One of the validated candidate genes identified through the pooled shRNA screen was DOK2, an adapter protein downstream of tyrosine kinase, which has been shown by others to be a lung cancer tumor suppressor. We show that suppression of DOK2 by short hairpin RNAs in ovarian cell lines conferred resistance to platinum treatment. To elucidate the mechanism for resistance, we measured the influx of platinum into the cells using C-14 tagged carboplatin. As a result, uptake of carboplatin was found to be decreased with DOK2 suppression. Consistent with DOK2 having tumor suppressor activity, knockdowns in ovarian cell lines increases growth and migration. Furthermore, loss of DOK2 induces invasive and tumorigenic phenotypes in ovarian cell lines. DOK2 is already a proven tumor suppressor in lung cancer, and our experiments indicate DOK2 has tumor suppressor features in ovarian cancer as well. We show that DOK2 is a tumor suppressor in ovarian cancer and that the loss of DOK2 also contributes to platinum resistance. Understanding DOK2 function will help us understand ovarian cancer development, progression as well as therapy resistance.