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Abstract 2988: DOK2 suppression by methylation induces platinum resistance via suppression of apoptosis in ovarian cancer cells.

Noelle L. Cutter Ph.D.
Molloy College, ncutter@molloy.edu

Elena Lum

Michelle Vigliotti

Nilanjana Banerjee

Sitharthan Kamalakaran

See next page for additional authors

Authors

Noelle L. Cutter Ph.D., Elena Lum, Michelle Vigliotti, Nilanjana Banerjee, Sitharthan Kamalakaran, Kazimierz O. Wrzeszczynski, Sohail Khan, Nevenka Dimitrova, Douglas A. Levine, and Robert Lucito

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Abstract

Ovarian cancers are highly heterogeneous and while chemotherapy is the preferred treatment, many patients are intrinsically resistant or quickly develop resistance. Furthermore, all tumors that recur will become resistant. Recent evidence suggests that epigenetic deregulation may be a key factor in the onset and maintenance of chemoresistance. To examine the ovarian epigenome, we first analyzed a set of 43 primary ovarian tumors and 9 normal ovarian samples. Since therapy response is a significant issue for ovarian cancer patients we analyzed the epigenetic differences that segregate with platinum response. We then associated expression data to identify genes with expression changes potentially altered by promoter methylation to generate a list of candidate platinum resistance genes. Next, we developed a tissue culture carboplatin resistance screen to determine which candidates functionally affect resistance. The screen utilized pools of shRNAs of the candidate genes to identify genes that when repressed allowed survival from carboplatin treatment, in order to validate that our epigenetics screen identified genes involved in resistance. Of the genes identified in the screen we further characterized one gene, docking protein 2 (DOK2), an adapter protein downstream of tyrosine kinase, to determine if we could elucidate what mechanism was used to increase resistance. Our analysis determined that loss of DOK2 decreased the level of apoptosis in response to carboplatin. In addition, we determined that in cells with reduced DOK2, the level of anoikis was decreased, a mechanism of possible importance in ovarian cancer where there is a large number of cells floating in ascites. Functional analysis of the DOK2 genes ability to affect resistance validates this approach to finding genes involved in carboplatin resistance.