Talk presented by Dr. Aaron R. Quinlan
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How do ovarian cancers acquire resistance to chemotherapy?

Abstract

Ovarian cancer accounts for 250000 new cancer cases each year worldwide and it has the highest mortality rate among gynecological malignancies. This is owing to the fact that most patients are diagnosed with advanced stage disease, and despite initial response to chemotherapy, the vast majority eventually develop chemoresistant disease. Standard treatment of ovarian cancer consists of surgical resection followed by chemotherapy using platinum and taxane based combination regimens. Platinum drugs (cisplatin and carboplatin) have been the most active agents for the treatment of ovarian cancer for the last four decades and the prognosis for women with ovarian cancer is closely related to their response to platinum agents. While 75-80% of patients with ovarian cancer initially respond to platinum-based chemotherapy, the majority develop acquired platinum resistance. The molecular origins this acquired chemoresistance are very poorly understood and furthermore, patients with platinum resistant disease also have poor response rates to other chemotherapeutic agents.

By deeply (>200X coverage) sequencing the exomes of normal tissue and both chemonaive and chemoresistant tumors from 14 patients (FFPE blocks), we explore the clonal evolution of ovarian cancer in response to common platinum-based chemotherapy. Our analyses provide crucial insight into whether resistance is conferred by either an intrinsically resistant subclonal population or, ironically, from new mutations that arise as a consequence of the DNA damaging agents that are used to treat the primary tumor. We investigate the mutational landscape of both chemonaive and chemoresistant tumors and apply phylogeny techniques to infer the clonal evolution of the tumors in response to chemotherapy. Our analyses thus far demonstrate dramatic evolutionary changes in resistant tumors. The data we present yield insight into the common genes and pathways that drive resistance and hint at future personalized therapies that target the affected genes in a given patient's resistant clonal populations.