Ovarian Cancer Genomics: Biological insights from next-generation sequencing of cancer genomes

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Due to its advanced stage at presentation, high-grade serous (HGS) ovarian cancer has been proposed as arising *de novo* from putative precursor lesions in the Fallopian tube and progressing rapidly to advanced disease. Using multi-region sequencing of tumor transcriptomes, we first identified mutations present in 9 spatially discrete tumor implants from each patient. The results of this analysis indicate less than 5% of mutations are shared across nine tumor implants, suggesting high levels of tumor heterogeneity in each patient. Using common and unique mutations found at these tumor implants, we reconstructed phylogenetic trees to establish the ancestral relationship among tumor implants. The results of this analysis indicate that in two patients peritoneal metastases arose from early branching events that preceded branching events for ovarian carcinomas and that in the other two patients peritoneal metastases and ovarian carcinomas arose concurrently. Finally, we used mutation frequencies to infer tumor subclones within each tumor implant. The results of this analysis indicate that dominant ancestral subclones were present in both ovarian carcinomas and peritoneal metastases. In addition, subclone analysis showed two unique patterns of evolution where one ancestral subclone was limited to the ovary and the other ancestral subclone, driven by *TP53* mutation, underwent clonal expansion and produced the major extent of disease including peritoneal metastases. These results support the extra-ovarian origin and provide the first genetic evidence for early peritoneal metastases that often precede ovarian carcinomas in HGS ovarian cancer.