Genomic instability and evolution in high-grade serous ovarian cancers

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Abstract: Over 50% of high grade serous ovarian cancers (HGS) have defective homologous recombination (HR) function. However, the remaining cases have no known genomic instability mechanisms. Here we present the genomic landscapes and their evolution in a model system of two pairs of divergent clones established from three cases of HGS, by next-generation genome and exome sequencing. Both tumours exhibited consistent patterns of rearrangements within their matched pairs but were distinct from each other, suggesting that they each had distinct instability mechanisms. The first tumour, with known HR defect, carried high proportion of inter-chromosomal breakpoints and small (~13kb) deletions, where junctions showed evidence of non-homologous end-joining repair. The second pair contained >200 tandem repeats throughout the genome, with a median size of ~350kb. We further showed that this tandem duplicator phenotype arose early in carcinogenesis and was persistent throughout the evolution of this tumour. Using the non-linear nature of progression of these tumour pairs, we deduced the chronology and predicted the functional consequences of mutations, including point mutations, indels and rearrangements, and were able to shortlist candidate initiating mutations in these tumours.