Dissecting the role of Copy Number Alterations as Drivers of Immune Evasion in Ovarian Cancer

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High-grade serous ovarian cancer (HGSOC) is the most lethal gynecologic malignancy, with a mortality rate of 70% due to limited response to available therapies, representing a major unmet clinical need. Genetically, this disease is characterized by almost universal inactivation of the tumor suppressor TP53 and an unusually high rate of copy number alterations (CNAs). Emerging evidence indicates that high CNA burden is associated with altered anti-tumor immune responses and immune evasion across cancer types, suggesting that recurrent chromosomal deletions may functionally impact tumor-immune interactions. Consistently, HGSOC shows limited clinical benefit from immune checkpoint blockade, indicating that tumor-intrinsic genomic alterations may impair immune recognition. However, the direct functional impact of CNAs to HGSOC immune evasion remains poorly understood, which is due to a lack of suitable models, and the challenges in manipulating large genomic regions.

To address this knowledge gap we combine two complementary approaches: the generation of novel genetically defined immunocompetent HGSOC models, and the use of MACHETE (Molecular Alteration of Chromosome with Engineered Tandem Elements) for CNA engineering. Immunocompetent models were generated via CRISPR-Cas9 knockout of one or more HGSOC-related tumor suppressor genes (*Trp53*, *Pten*, and *Nf1*) on isolated ovarian cells. Edited cells were expanded and implanted in the ovarian bursa of immunocompetent hosts, resulting in efficient tumor formation when using triple knockout cells. Tumors were characterized by histology, flow cytometry, and single cell RNA Seq, demonstrating that the model recapitulates key histopathological, transcriptomic, and immunological features of ovarian cancer. This validated platform provides a tractable framework for MACHETE-mediated engineering of recurrent chromosomal deletions to investigate their role in tumor evolution and immune evasion in HGSOC.