Modifiers of BRCA2 tumor suppressor loss of function: FIGNL1 as an anti-recombinase

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Abstract**:** Genomic instability is one of the hallmarks of cancer cells. Several well-known tumor suppressors are involved in the DNA damage response, and, significantly, therapeutic approaches and treatment outcomes, including development of resistance to chemotherapy, can be determined by the state of the cellular DNA damage response pathways. In this application, we focus on the tumor suppressor BRCA2 which plays critical roles in the homologous recombination (HR) pathway of DNA repair, considered to be a particularly error free pathway of repair, and replication fork protection, which protects nascent strands at stalled replication forks from degradation. BRCA2 was discovered as a breast and ovarian cancer suppressor but its role in other cancers, e.g., metastatic castration resistant prostate cancer (mCRPC), has recently been uncovered. Loss of BRCA2 in normal cells leads to replication stress and cell death, while in tumor cells, BRCA2 loss leads to genomic instability and tumorigenesis. This project aims to identify factors that modify the cellular response to BRCA2 loss in both cellular contexts, including those factors that are druggable.