ID 07.1
Specific killing of BRCA1-deficient cancer cells by depletion of EXO1

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BRCA1 and BRCA2 are essential genome maintenance factors that function in the repair of DNA Double-Strand Breaks (DSBs) by homologous recombination (HR). Cancer patients that carry tumors with loss-of-function mutations in BRCA1 or BRCA2 often benefit from treatment with PARP inhibitor therapy, which specifically kills HR-deficient tumor cells. However, clinical responses are rarely long-lasting due to resistance to PARP inhibitor treatment. We therefore sought to identify novel therapeutic opportunities to treat HR-deficient tumors. Our studies revealed that genetic inactivation of the exonuclease EXO1 is severely toxic to BRCA1-deficient cells, but not to BRCA1-proficient cells. Mechanistically, our data suggest show that loss of EXO1 results in DSB formation, potentially due to a defect in the maturation of Okazaki fragments. BRCA1/EXO1 double-deficient cells are severely compromised in their capacity to repair these DSBs, resulting in genomic instability and cell death. Taken together, we have uncovered EXO1 as a novel synthetic lethal target with therapeutic potential to treat patients carrying BRCA1-deficient tumors.