ABSTRACT

In this project mechanisms of PARP inhibitor (PARPi) resistance due to alterations in the DNA damage response have been explored in mouse BRCA1-deficient mammary tumors that are deficient in homology-directed DNA repair. The overall goal was to understand the mechanisms that impair the efficacy of PARP inhibition and thereby find new therapeutic strategies that may improve current therapies. Thus far olaparib is the only PARP inhibitor that has been approved by both the EMA and FDA as therapy for BRCA-mutated ovarian cancer. In mouse models for BRCA1- or BRCA2-associated breast cancer high sensitivity of the tumors to the PARPi olaparib was found. Despite the initial sensitivity, tumors were not eradicated and eventually acquire olaparib resistance. This provides a useful preclinical model to investigate mechanisms of PARPi resistance. As analytical tool I focused on using loss-of-function shRNA screens in cell lines derived from the BRCA1-deficient mouse mammary tumors. My aim was to identify genes that cause resistance when deleted. In particular I was interested in genes that encode proteins involved in the DNA damage response.