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Epigenetically Down-Regulated BRCA2 through Acetyltransferase KAT2B Increases the Sensitivity of Colorectal Cancer to Olaparib

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Olaparib suppresses DNA damage repair by inhibiting the poly ADP ribose polymerase (PARP), especially in cancers with BRCA1/2 mutations or the BRCA-ness phenotype. However, the first trials showed that some patients with defective DNA damage repair are still resistant to olaparib. The recovery of the wildtype BRCA is a prominent mechanism of PARP inhibitor (PARPi) resistance in BRCA-deficient tumors, but additional molecular features of olaparib resistance remain poorly understood. The objective of our study was to find molecular parameters that contribute to olaparib response or resistance in CRC. We report that histone acetyltransferase KAT2B decreases BRCA2 expression by reducing the acetylation of the 27th amino acid in histone H3 (H3K27) at the promoter of the BRCA2 gene in colorectal cancer (CRC). This increases the sensitivity of CRC cells toward olaparib treatment. The H3K27ac binding domain of BRCA2 may be required for its transcription. Low endogenous KAT2B expression, which we identify in a subset of cultured BRCA2-expressing CRC cells, leads to an accumulation of γH2AX (more DNA damage), resulting in low PARPi resistance in BRCA-expressing cells. Our results reveal KAT2B and histone acetylation as regulators of BRCA2 expression and PARPi responses in BRCA2-expressing CRC cells, providing further insights into molecular prerequisites for targeting BRCA-functional tumors.