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BCL2-overexpressing prostate cancer cells rely on PARP1-dependent end-joining and are sensitive to combined PARP inhibitor and radiation therapy

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Abstract

Here we report that BCL2 blocks DNA double strand break (DSB) repair via nonhomologous end-joining (NHEJ), through sequestration of KU80 protein outside the nucleus. We find that this effect is associated with a repair switch to the error-prone PARP1-dependent end-joining (PARP1-EJ). We present *in-vitro* proof-of-concept for therapeutic targeting of this switch using PARP inhibitor to specifically enhance the radiosensitivity of BCL2-overexpressing cells. Given its erroneous behavior, PARP1-EJ might allow for the accumulation of genetic alterations and tumor progression. Consistently, we report an inverse correlation between BCL2 expression and biochemical recurrence-free survival of 10.259 prostate cancer (PCa) patients who underwent primary radical-prostatectomy for localized disease. Further, we evaluated retrospectively the impact of BCL2 expression on clinical outcome of 1.426 PCa patients, who had been given salvage radiotherapy at relapse after radical prostatectomy. In line with its role in blocking NHEJ, BCL2 over-expressers showed significantly better response to salvage radiotherapy compared to low-expressers.

Collectively, our findings identify BCL2 status in PCa as a putative predictor of (i) radiotherapy response and (ii) response to treatment with PARP inhibitor olaparib as a radiosensitizing agent.

Keywords: BCL2, DNA double strand break repair, nonhomologous end-joining, KU, prostate cancer, PARP inhibition, radiosensitization