

PARP1-mediated E2F1 regulation of DNA repair capacity

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Background: PARP1 holds two major functions on chromatin, DNA damage repair and transcriptional regulation, both of which are relevant in the context of cancer. Notably, PARP1 has been found to be a key modulator of androgen receptor (AR) function and AR-dependent phenotypes, which is a driving factor in prostate cancer (PCa) biology and therapeutic management. Recent studies indicate an unanticipated prevalence of DNA repair alterations in advanced PCa and showed that PARP1 inhibitors (PARPi) can effectively manage a subset of these tumors. Despite the functions of PARP1 in DNA repair having been exploited as a therapeutic target for tumors with *BRCA1/2* aberrations, factors beyond DNA repair alterations clearly play a role in the response to PARPi. Notably, in the TO-PARP trial, not all patients with DNA repair aberrations responded to PARPi; conversely, tumors lacking *BRCA1/2* or other DNA repair alterations show objective response to PARPi in PCa and other tumor types. These clinical data suggest that the genetic (e.g. BRCA-ness) and pharmacologic interplay is complex in the context of PARPi. Given the preclinical and clinical data, pursuing a deeper understanding of the molecular underpinnings of PARPi action in PCa may yield significant benefit. **Methods:** Genome-wide transcriptional profiling in response to PARPi was performed and the PARP1-regulated transcriptome was identified. **Results:** Both the PARP1-regulated transcriptome, as well as PARP1 enzymatic activity were found to be elevated as a function of PCa progression. Further interrogation of the PARP1-regulated transcriptome revealed a major impact on E2F1-regulated genes, and chromatin immunoprecipitation analyses indicated that PARP1 functions to regulate the chromatin architecture and E2F1 occupancy at E2F1 target gene loci. Most prominent among the E2F1-regulated genes responsive to PARPi were genes associated with DNA damage repair, with a particular enrichment for genes involved in homologous recombination (HR). **Conclusions:** In sum, these data indicate PARP1 regulates function of key oncogenic transcription factors (AR and E2F1) in PCa, and part of the effect of PARPi may be through down-regulation of DNA repair factors.

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