PARP-1 and E2F1 collaborate to transcriptionally regulate DNA repair factor availability

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PARP-1 holds at least four major functions on chromatin: DNA damage repair, telomeric maintenance, chromatin dynamics, and transcriptional regulation, all of which are relevant in the context of cancer. Notably, PARP-1 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 PARP-1 inhibitors (PARPi) can effectively manage of a subset of these tumors. Despite the functions of PARP-1 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, while DNA repair defects enrich for PARPi responders, *BRCA1/2* alterations do not appear to be necessary nor sufficient to induce PARPi clinical response. Given the preclinical and clinical data, pursuing a deeper understanding of the molecular underpinnings of PARPi action in PCa may yield significant benefit. Human tissue microarrays were utilized to quantify PARP-1 levels and activity as a function of PCa progression. Genome-wide transcriptional profiling in response to PARPi was performed and the PARP-1-regulated transcriptome was identified. Both the PARP-1-regulated transcriptome, as well as PARP-1 enzymatic activity, were found to be elevated as a function of PCa progression. Further interrogation of the PARP-1-regulated transcriptome revealed a major impact on E2F1-regulated genes, and chromatin immunoprecipitation analyses indicated that PARP-1 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). In sum, these data indicate PARP-1 regulates the 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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