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

Mathew J. Schiewer1,6, Amy Mandigo1,6, Nick Gordon1,6, Fangjin Huang12, Gaur Sanchaika12, Shuang Zhao7, Joseph Evans7, Sumin Han7, Theodore Parsons5,6, Ruth Birbe5,6, Peter McCue5,6, Tapio Visakorkpi8, Ganesh Raj9, Mark Rubin10, Johann de Bono11, Costas Lallas2,6, Edouard Trabulsi2,6, Leonard G. Gomella2,6, Adam P. Dicker3,6, Wm. Kevin Kelly4,6, Beatrice Knudsen12, Felix Y. Feng13, and Karen E. Knudsen1,2,3,6


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 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.

Conflict of Interest: None to report
Funding sources: PCF Young Investigator Award to MJS and PCF Challenge Award to KEK