A Multi-omic Characterization of PARP Enzymes in Cancer to Identify Novel monoPARP Drug Targets

Ryan P. Abo*, Mario Niepel, Heike Keilhack
Address: 35 Cambridgepark Drive, Suite 300, Cambridge MA, 02140
*Correspondence to rabo@ribontx.com

Abstract 4381
AACR 2020

INTRODUCTION

The poly-ADP-ribose polymerases (PARPs) are a family of 17 enzymes with conserved catalytic domains. They regulate a wide variety of important cellular processes including cellular stress signaling pathways implicated in inflammation and cancer.

Much of the PARP research has been dedicated to the four polyPARPs (PARP1, 2, 5a, and 5b) which transfer poly-ADP-ribose chains on their target proteins. In particular, the critical role of PARP1/2 in DNA damage response and repair has been studied extensively (see Figure 2), leading to effective cancer therapies. However, the majority of PARPs are monoPARPs, which transfer a single ADP-ribose to their target proteins. Recently, several of these family members have emerged in the literature as playing cancer-specific roles.

PARP Family

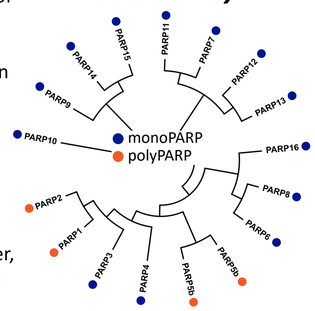


Figure 1. Dendrogram illustrating PARP family enzyme genetic sequence alignment**.**

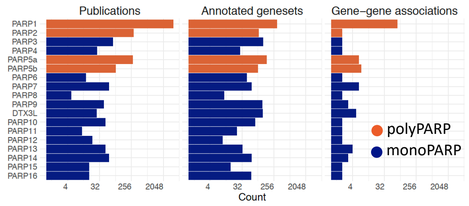
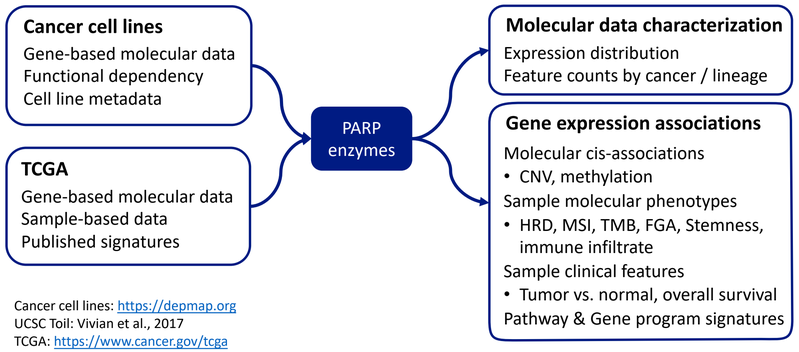


Figure 2. Bar plots showing the number of publications, annotated gene sets and gene-gene associations for the PARP enzymes. polyPARPs account for the majority of research and annotation.

We set out to characterize the molecular features of PARPs and their role in human cancer by mining the deep collection of publicly available molecular data from primary cancer, normal tissue samples and cancer cell lines. We explored standard oncogene hypotheses for all the PARPs, including mutational hotspots, copy-number variations, tumor mRNA overexpression, survival associations to genomic or expression variation, and cancer cell line dependency.

Our results provide the first pan-cancer *in silico* characterization of the PARP family, revealing a broad molecular and potential mechanistic diversity among the PARPs across cancer.

WORKFLOW & DATA



Cancer cell lines: https://depmap.org
UCSC Toil: Vivian et al., 2017
TCGA: https://www.cancer.gov/tcga

RESULTS

PARPs in Cancer Genome Atlas

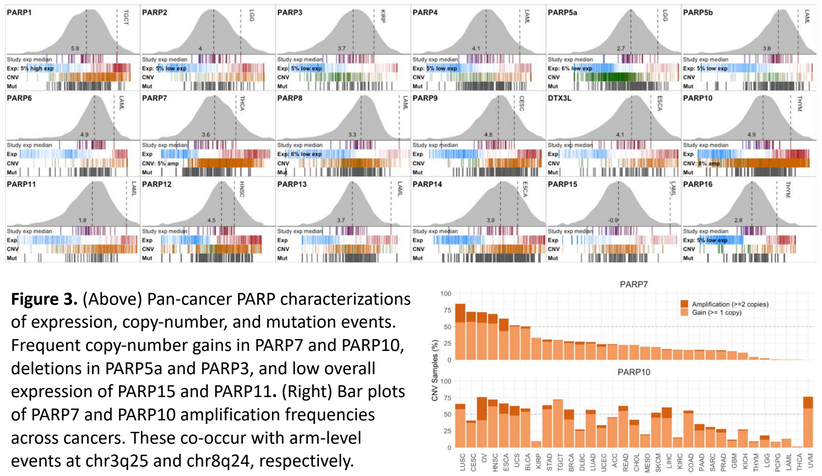


Figure 3. (Above) Pan-cancer PARP characterizations of expression, copy-number, and mutation events. Frequent copy-number gains in PARP7 and PARP10, deletions in PARP5a and PARP3, and low overall expression of PARP15 and PARP11**.** (Right) Bar plots of PARP7 and PARP10 amplification frequencies across cancers. These co-occur with arm-level events at chr3q25 and chr8q24, respectively.

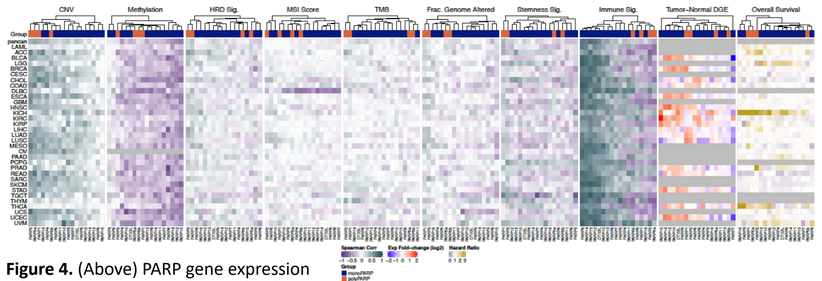


Figure 4. (Above) PARP gene expression correlations across cancers show CNV and methylation as potential expression predictors across cancers. PARP1/2 are consistently correlated with HRD, MSI, TMB, FGA and stemness phenotypes, while a subset of monoPARPs have strong immune signature correlations and over-expression patterns.

Figure 5. (Below) Alluvial plot illustrates the positive PARP gene expression correlations with immune signatures by cancer type. Each line represents an aggregate significance of correlation between gene expression and immune signatures (Wolf et al. 2014).

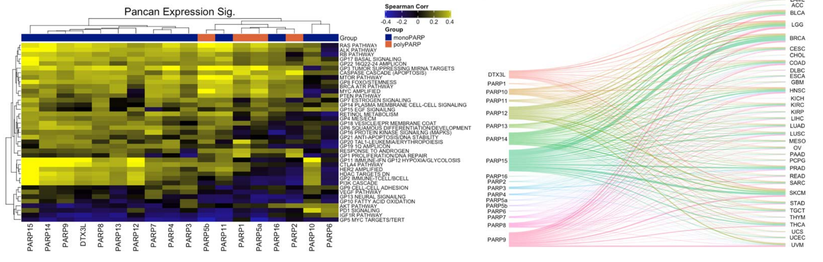


Figure 6. (Above) Heatmap of the mean correlation across cancers between gene expression and pancan gene program signatures (Hoadley et al. 2014). A consistent positive correlation between expression and gene signatures observed for PARP family pan-PARP negative correlations with MYC target/TERT and IGF1R pathway signatures. A strong subset of positive correlations with a subset of PARPs and immune signatures (GP2 Immune-Tcell/Bcell, CTLA4 Pathway, GP11 Immune-IFN).

PARPs in Cancer Cell Lines

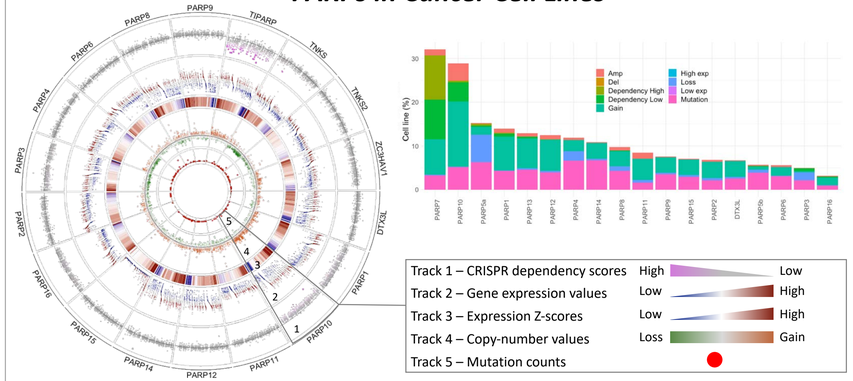


Figure 7. PARP expression, CNV, mutation and CRISPR dependency scores are plotted across cancer cell lines**.** In line with the primary tumor data in TCGA, the PARPs have few oncogenic events, aside from the copy-number gains in PARP7 and PARPP10. The majority of the PARPs show no dependencies across cell lines in Depmap (in vitro proliferation-based screen), other than PARP7 and PARP10.

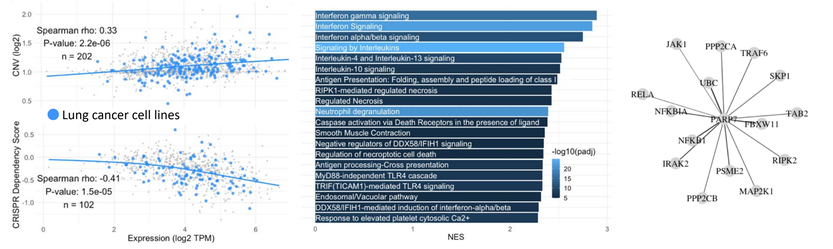


Figure 8. Biplots between PARP7 expression and PARP7 copy-number values (top-left) and CRISPR dependency scores (bottom-left). Lung cancer cell lines are highlighted in blue with the Spearman correlations between the molecular values, further indicating a role for PARP7 in lung cancer. (Middle) A bar plot of the top 20 gene set enrichment results using PARP7 positively co-expressed genes from lung cancer cell lines. There is a significant enrichment of innate immune and interferon-related gene sets and pathways. (Right) A network graph highlighting the 15 most frequent genes in the leading edges of immune-related co-expression enriched gene sets.

CONCLUSIONS

Our results provide the first pan-cancer *in silico* characterization of the PARP family, revealing a broad molecular and potential mechanistic diversity among the PARPs across cancer. Notwithstanding the lack of traditional oncogenic features, such as mutational hotspots, in the PARPs, our analyses highlight several monoPARPs with potential oncogenic roles and further support our focus of targeting these in the clinic (e.g., PARP7).

The high-level, multi-omic analyses in primary tumors and cancer cell lines presented here further distinguish the polyPARPs and monoPARPs and help guide additional hypotheses to further explore for a number of the monoPARPs. Specifically, there is a subset of the monoPARPs (PARP9, PARP10, PARP12, PARP14, PARP15) with strong immune signature associations across cancers, suggesting potential roles in the tumor microenvironment.

Future datasets with treated tumor samples, refined single-cell measurements, and more molecular phenotyping will further elucidate the role of the PARP family in cancer.