PARP-1 regulates DNA repair factor availability

Matthew J. Schiewer[1,7], Amy C. Mandigo[1,7], Nicolas Gordon[1,7], Fangjin Huang[12], Sanchaika Gaur[12], Renée de Leeuw[1,7], Shuang G. Zhao[8], Joseph Evans[8], Sumin Han[8], Theodore Parsons[5,7], Ruth Birbe[9], Peter McCue[5,7], Christopher McNair[1,7], Saswati N. Chand[1,7], Ylenia Cendon-Florez[1,7], Peter Gallagher[1,7], Jennifer J. McCann[1,7], Neermala Poudel Neupane[1,7], Ayesha A. Shafi[1,7], Emanuela Dylgjeri[1,7], Lucas J. Brand[1,7], Tapio Visakorpi[10], Ganesh V. Raj[11], Costas D. Lallas[2,7], Edouard J. Trabulsi[2,7], Leonard G. Gomella[2,7], Adam P. Dicker[3,7], Wm. Kevin Kelly[4,7], Benjamin E. Leiby[6,7], Beatrice Knudsen[12], Felix Y. Feng[13], and Karen E. Knudsen[1,2,3,4,7]

Departments of Cancer Biology[1], Urology[2], Radiation Oncology[3], Medical Oncology[4], Pathology[5], Pharmacology and Experimental Therapeutics[6], and Sidney Kimmel Cancer Center[7], Thomas Jefferson University. Department of Radiation Oncology, University of Michigan[8]. Cooper University Health[9], University of Tampere[10]. UT Southwestern[11]. Cedars-Sinai Medical Center[12]. Departments of Radiation Oncology, Urology, and Medicine, University of California, San Francisco[13].

Background: PARP-1 holds major functions on chromatin, DNA damage repair and transcriptional regulation, both of which are relevant in the context of cancer. Methods and Results: Here, unbiased transcriptional profiling revealed the downstream transcriptional profile of PARP-1 enzymatic activity. Further investigation of the PARP-1-regulated transcriptome and secondary strategies for assessing PARP-1 activity in patient tissues revealed that PARP-1 activity was unexpectedly enriched as a function of disease progression and was associated with poor outcome independent of DNA double-strand breaks, suggesting that enhanced PARP-1 activity may promote aggressive phenotypes. Mechanistic investigation revealed that active PARP-1 served to enhance E2F1 transcription factor activity, and specifically promoted E2F1-mediated induction of DNA repair factors involved in homologous recombination (HR). Conversely, PARP-1 inhibition reduced HR factor availability and thus acted to induce or enhance "BRCA-ness". Conclusions: These observations bring new understanding of PARP-1 function in cancer and have significant ramifications on predicting PARP-1 inhibitor function in the clinical setting.

Conflict of Interest: The authors declare no conflicts of interest

Funding Acknowledgement: PCF YI Awards (MJS, RdL, AAS), PCF Challenge Award (WKK, FYF, KEK)