Circadian clock gene \textit{PER1} mutation in colorectal cancer (CRC)

Francesca Battaglini$^{1,2}$, Joanne Xiux$^{3}$, Michelle Winnerp$^{1}$, Richard M. Goldberg$^{3}$, Philip A. Philip$^{4}$, Andreas Seeber$^{2}$, Alberto Puccini$^{5}$, Ryuma Tokunaga$^{1}$, Madhia Naseem$^{1}$, Shivini Somi$^{1}$, Michelle McLain$^{1}$, Martin D. Berger$^{2}$, Afshaneh Barzi$^{1}$, Wu Zhang$^{1}$, Jimmy J. Hwang$^{7}$, Anthony F. Shields$^{5}$, John L. Marshall$^{2}$, W. Michael Korn$^{1}$ and Heinz-Josef Lenz$^{1}$

$^{1}$Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. $^{2}$Clinical and Experimental Oncology Department, Veneto Institute of Oncology IRCCS-VIDO, Padua, Italy. $^{3}$Ciris Life Sciences, Phoenix, AZ $^{4}$West Virginia University Cancer Institute, Morgantown, WV, USA. $^{5}$Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA. $^{6}$Department of Hematology and Oncology, Timon Cancer Research Institute, Infirmary Medical Health System, Katowice, Poland. $^{7}$Lewis Cancer Institute, Carolinas HealthCare System, Charlotte, NC.

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Introduction

• The clock machinery regulates the circadian expression of up to 20% of genes expressed in any particular cell or tissue, modulating key cellular pathways including cell proliferation and apoptosis; DNA repair; cellular senescence; metabolic homeostasis; inflammation and immune response$^{1}$.

• Colorectal carcinogenesis and CRC progression have been linked to the disruption of the molecular clockwork by experimental data showing deregulation of the circadian machinery and circadian gene expression, both in preclinical models and in colon neoplastic tissue$^{2}$.

• PER1 encodes for one of the main negative regulators of the clock machinery$^{3}$, with an apparent tumor-suppressor role suggested by in vivo studies and in vitro evidence$^{4,5}$.

• Downregulation of PER1 has been observed in CRC samples compared to matched healthy tissues, and lower expression levels of PER1 have been associated with poor survival and increased incidence of liver metastases$^{6,7}$.

• Few data are available on \textit{PER1} gene mutations (\textit{PER1} mut) in CRC. Therefore, we aimed to explore the clinical and molecular differences between \textit{PER1} mutated versus wild-type (WT) CRCs.

Methods

• A cohort of 409 CRCs tested with comprehensive genomic profiling by Ciris Life Sciences (Phoenix, AZ) was identified from a retrospective database and included in this analysis.

• NextSeq sequencing (IHC) was performed for 93 genes isolated from formalin-fixed paraffin-embedded tumor samples using the NextSeq platform (Illumina, Inc., San Diego, CA) on the Ciris Sequat.

• Microsatellite instability high (MSI-H) status was tested by NSI in 2966 tumors. The threshold to determine MSI-H was determined to be 46 or more microsatellite loci with somatic insertions or deletions to generate a sensitivity of greater than 95% and specificity of greater than 99%. NSI (43-, 45-, or 47-mie) resulted in microsatellite unstable (MSI-H), 42 loci$^{8}$.

• Pathogenicity of \textit{PER1} mut was estimated using Poly-Phen$^{9}$, SIFT and PROVEAN scores.

• \textit{PER1} mut prevalence comparisons in each groups were performed using Fisher-Exact test, while Chi-square deviance test (i.e. likelihood ratio test) on nested logistic regression models was performed for multiplicative analysis. \(P<0.05\) was considered statistically significant for all tests performed.

• Overall, 1.55 unique \textit{PER1} variants were identified in 343 samples (7.4%), 45 were classified as pathologically/possibly pathologic (\textit{PER1} mut; \textit{per}) according to predictive scores. \textit{PER1} mut were significantly associated with right-tumor location (\textit{p}<0.001) and MSI-H (\textit{p}<0.001).

• Overall incidence of \textit{PER1} mut and PATHmut in the MSI-H group were 24% and 3.4%, respectively.

• In the multivariate analyses \textit{PATH} mut were independently associated with mutations in \textit{ARAF}, \textit{BAP1}, \textit{CHEK2}, \textit{NF1}, \textit{PIK3CA} and \textit{POLE}.

Results

1. Basic characteristics of the 4097 tumors interrogated for \textit{PER1} mutation status.

2. \textit{PER1} mutation rates in different groups. P values of significant differences are shown.

3. \textit{PER1} mut and \textit{PATH} mut were significantly \textit{per} associated with additional markers. Shown are significant results after multivariate analysis.

Conclusions

• Our results provide the first exploratory data on \textit{PER1} mut association with clinical and molecular features in CRC, in a large population of patients extensive genetic testing.

• A deeper understanding of \textit{PER1} mut pathogenicity and functional role is necessary to guide future analyses. Nevertheless, our results suggest a significant association with MSI-H, possibly reflecting an interference between mismatch repair status and the circadian clock gene pathway in CRC, consistent with previous data and warranting further investigation.

References