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PARP1 Is Overexpressed in Hematological Malignant Cell Lines: A Framework for Experimental Oncology

CAIO BEZERRA MACHADO*, EMERSON LUCENA DA SILVA*, BEATRIZ MARIA DIAS NOGUEIRA, MANOEL ODORICO DE MORAES FILHO, RAQUEL CARVALHO MONTENEGRO, MARIA ELISABETE AMARAL DE MORAES and CAROLINE AQUINO MOREIRA-NUNES

Pharmacogenetics Laboratory, Drug Research and Development Center (NPDM), Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, Brazil

Abstract. *Background/Aim: Experimental oncology commonly uses cells as oncological models, providing a framework for the testing of drugs, and investigation of cytotoxicity, mutagenesis and carcinogenesis. Investigations into poly-ADP-ribose polymerase 1 (PARP1) inhibition have become ever more relevant due to its approval as a therapeutic option for tumors with BRCA1/2 DNA repair-associated mutation and the seemingly high PARP expression levels in some tumor subtypes. In this study, we aimed to determine PARP1 gene expression of different hematological cancer-derived cell lineages and compare them to that of normal cell lines. Materials and Methods: PARP1 gene expression in seven different neoplastic lineages, representing three different hematological disorders (chronic myeloid leukemia, Burkitt lymphoma and acute lymphoblastic leukemia), was quantified by quantitative real-time polymerase chain reaction. Results: All hematological malignant lineages in this study overexpressed PARP1 when compared to the normal cell line MRC-5, with Burkitt's lymphoma cells having the highest expression values (fold change: 93). Conclusion: Overexpression of PARP1 in hematological malignant lineages is a finding of crucial importance to future studies exploring possible cellular oncogenic pathways and supports investigations into the effectiveness of PARP1 inhibitors against hematological disorders.*

*These Authors contributed equally to this work

Correspondence to: Caroline Aquino Moreira-Nunes, Federal University of Ceará, Coronel Nunes de Melo st, n 1000, Rodolfo Teófilo, CEP: 60416-000 Fortaleza, CE, Brazil. Tel.: +55 8533668033, e-mail: carolfam@gmail.com

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Experimental oncology consists in the use of cell cultures for the study and investigation of neoplasms in biological models. Commonly utilized in research laboratories, cell models represent an excellent basis for analyses of genetic and epigenetic molecular alterations and anticancer drug testing (1, 2).

Research studies utilizing cell lineages are demonstrated to be appropriate frameworks for the development of new drugs and provide credible models for the analyses of cytotoxicity, mutagenesis and carcinogenesis, also allowing for consistent and reproducible results (3). The primary advantage when working with cell lines is the availability of a potentially unlimited source of biological material, as cells are able to divide and grow indefinitely *in vitro*. Moreover, the possibility of storing cells in liquid nitrogen allows for continuation of research over prolonged periods (4).

Investigations into poly-ADP-ribose polymerase (PARP) cellular pathways have become ever more relevant since the first approval of PARP inhibitors (PARPi) for the treatment of breast cancer 1/2 (*BRCA1/2*) DNA repair-associated-deficient tumors, with PARP1 being the main target of inhibition (5, 6). PARP1 plays a major role in the DNA-damage response and is overexpressed in various tumor subtypes, being mainly associated with an unfavorable prognosis (7-9).

PARPi are targeted antineoplastic drugs and the treatment outcome is dependent on PARP1 expression in the targeted cells (5, 10). In this study, we aimed to determine the PARP1 expression level of different cell lineages representing neoplastic hematological disorders and to compare them to the expression levels of normal cell lines, creating a basis for future studies of PARPi utilizing experimental oncology models.

Materials and Methods

Cell culture. For analyses of *PARP1* gene expression, we utilized a panel of leukemia and normal cell lines for comparison, as shown in Table I. Cells lines derived from patients with chronic myeloid leukemia (CML) K-562, vincristine-resistant derivative K562-

Table I. *Cell lines evaluated in this study.*

Cell line	Tissue of origin	Classification	Reference
K-562	Bone marrow chronic myeloid leukemia	Blast cells	11
K562-Lucena 1	Derived from K-562	Vincristine-resistant	12
FEPS	Derived from K-562	Daunorubicin-resistant	13
SUP-B15	Bone marrow	B Lymphoblast	14
Jurkat	Peripheral blood	T Lymphocyte	15
Namalwa	Peripheral blood	B Lymphocyte	16
Raji	Bone marrow	B Lymphocyte	17
MRC-5	Human fetal lung fibroblasts	Normal cell	18
MNP-01	Non-neoplastic gastric epithelium	Normal cell	19

Lucena 1, and daunorubicin-resistant derivative FEPS were generously donated by Professor Vivian M. Rumjanek from the Federal University of Rio de Janeiro, Brazil. SUP-B15 and Jurkat cell lines derived from lymphoblastic leukemia, as well as Namalwa and Raji cell lines from Burkitt's lymphoma, were kindly provided by Professor Lucas Eduardo Botelho de Souza from Regional Blood Center of Ribeirão Preto, University of São Paulo, Brazil.

All leukemia cell lines were cultivated in RPMI; for resistant cell lines K562-Lucena 1 and FEPS, media were also supplemented with 60 nM vincristine sulfate and 46 nM daunorubicin, respectively. Normal cell lines derived from the gastric epithelium (MNP-01) and lung fibroblast (MRC-5) were maintained in Dulbecco's modified Eagle's medium. All media were supplemented with 10% (v/v) fetal bovine serum (Gibco®, Carlsbad, CA, USA), 1% (v/v) penicillin (100 U/ml) and streptomycin (100 mg/ml) (Gibco®), and cells were conditioned in a 5% CO_2 air-humidified atmosphere at 37˚C.

Total mRNA isolation and cDNA synthesis. Cells were plated in 12-well plates at 5×10^4 cells/welI for normal cells (MRC-5 and MNP-01) and about 7×10^4 cells/well for leukemia cells. Cell lines were maintained until 80% confluency (~48 hours for normal cells and 44 to 48 hours for leukemia cells). After the cultivation time, cells were collected and RNA was extracted with TRIzol Reagent® (Invitrogen™ , Carlsbad, CA, USA) according to the manufacturer's instructions. After extraction, RNA concentration and quality were determined using NanoDrop (Thermo Scientific, Carlsbad, CA, USA) and 20 ng was used for cDNA confection using High-Capacity cDNA Reverse Transcriptase kit (Life Technologies, Carlsbad, CA, USA). cDNA was then stored at −20˚C until further expression analysis.

Analysis of PARP1 expression by quantitative real-time reverse transcriptase polymerase chain reaction (qPCR). Quantitative real-time PCR was performed using the Power SYBR Green PCR Master Mix kit (Applied Biosystems®, Foster City, CA, USA). Relative expression levels of *PARP1* (NM_001618.3) were normalized and determined using β-actin gene (*ACTB*; NM_001101.5) as an endogenous control. Primer efficiency was determined for all genes described. The detection method was the TaqMan® Gene expression assays system (Applied Biosystems) and qPCR was performed using QuantStudio® 5 Real-Time PCR system (Applied Biosystems). The experiments were performed in triplicate and the standard requirements for performing the technique were followed (20). For calculating the relative expression levels, the $2^{-\Delta\Delta CT}$ method was used (21), considering the sample from the normal cell line MRC-5 as the calibrator of the assays.

Statistical analysis. Assays were performed in triplicate and results are shown as the mean±standard deviation, the relative expression of *PARP1* in cell lines was compared to the expression in the MRC-5 sample by one-way analysis of variance followed by Bonferroni's post-test. Significant differences were considered with an interval of confidence of 95% ($p<0.05$). GraphPad Prism 5.01 software (Merck®, Darmstadt, Hesse, Germany) was used for data analysis and graph design.

Results

Firstly, when we compared the expression of *PARP1* in cell lines derived from CML with the normal cell line MRC-5 (Figure 1), all those analyzed presented gene expression enhanced by more than 10-fold (K-562 and FEPS: $p<0.0001$; and K562-Lucena 1: $p<0.05$). When compared among themselves, FEPS showed higher expression than K-562 and K562-Lucena 1, at around 50- and 90-fold, respectively ($p<0.0001$).

Next, we analyzed *PARP1* expression in cell lines derived from acute leukemia. Both SUP-B15 ($p<0.0001$) and Jurkat ($p<0.001$) presented a significant increase in *PARP1* expression when compared to normal cells (approximately 30- and 20-fold, respectively). However, when these cell lines were compared with each other, there was no difference in gene expression (Figure 2).

We also evaluated *PARP1* gene expression in cell lines derived from Burkitt's lymphoma (BKL); Namalwa, and Raji cell lines presented a 90-fold and 70-fold increase in *PARP1* expression, respectively ($p<0.0001$) when compared to normal cell MRC-5 (Figure 3), and did not differ statistically in *PARP1* gene expression when compared with each other.

Discussion

Cancer cell lines are commonly used in research laboratories due to their easy manipulation compared to *in vivo* models, and more ethically accepted usage (1). Even though the cellular genetic expression may diverge between similar lineages cultivated in different laboratories, it is

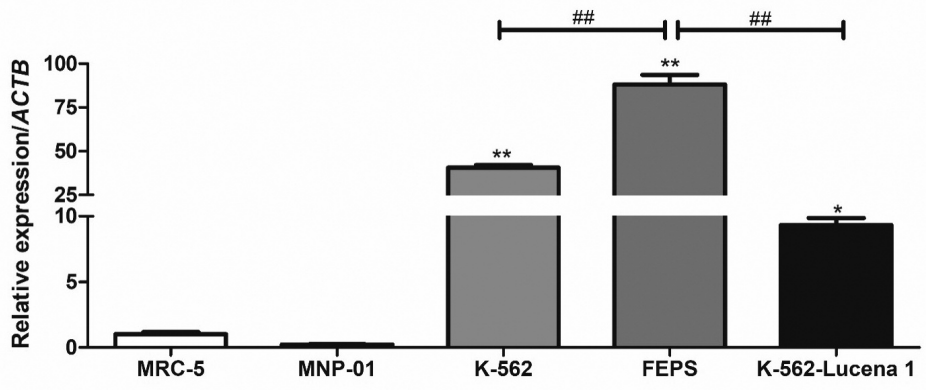

Figure 1. *Expression of poly-ADP-ribose polymerase 1 (PARP1) in chronic myeloid leukemia cell lines. Data are presented as the mean±SD of three independent experiments. PARP1 gene expression was normalized by endogenous gene actin beta (ACTB). Expression in normal gastric cells MNP-01, and chronic myeloid leukemia cell line K-562, its vincristine-resistant derivative K562-Lucena 1, and daunorubicin-resistant derivative FEPS was compared to that of lung fibroblasts MRC-5, using analysis of variance and multiple Bonferroni comparisons. Significantly different at: *p<0.05 and **p<0.0001 from MRC-5 cells; ##p<0.0001.*

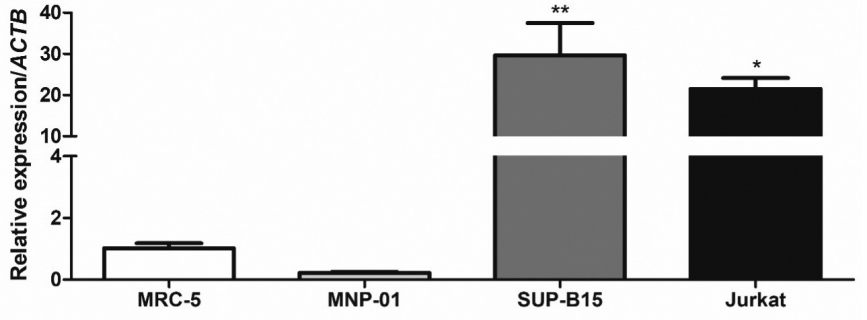

Figure 2. *Expression of poly-ADP-ribose polymerase 1 (PARP1) in acute leukemia cell lines. Data are presented as mean±SD of three independent experiments. PARP1 gene expression was normalized by endogenous gene actin beta (ACTB). Expression in normal gastric cells MNP-01 and cell lines of acute lymphoblastic leukemia (SUP-B15), and acute T-cell leukemia (Jurkat) was compared to that of lung fibroblasts MRC-5 using analysis of variance and multiple Bonferroni comparisons. Significantly different from MRC-5 cells at *p<0.001 and **p<0.0001.*

essential to determine a lineage's molecular profile for the correct conduction of anticancer drug tests and when searching for possible mechanisms of resistance (1, 22, 23).

Characterization of *PARP1* expression in cancer cell lines is becoming ever more relevant due to the increased use of PARPi in clinical practice for the treatment of different solid tumors and their promising activity in *in vitro* studies and clinical trials as a therapeutic option for leukemia and other hematological malignancies (24, 25).

When analyzing the profile of CML lineages, it is not surprising that significant differences in *PARP1* expression levels were detected, even though all lineages were derived from K-562, since previous literature reports already determined the main resistance mechanism of K562-Lucena 1 and FEPS to be through overexpression of ATP binding cassette subfamily B member 1 (*ABCB1*) transporter protein. More than 1,000 genes are differentially expressed between these cell lines (26), and we demonstrate *PARP1* to be one of these genes.

PARP1 was overexpressed in all CML lineages analyzed when compared to the normal MRC-5 cell line. This observation corroborates previous data indicating PARPi effectiveness against CML cell lines and patient samples harboring breakpoint cluster region–Abelson murine leukemia translocation (*BCR–ABL*), especially when combined in synergistic treatments (27-30).

Both acute leukemia lineages analyzed also demonstrate *PARP1* overexpression in comparison to normal cells. While PARPi usage may not always be effective as a single agent against acute leukemia cells (31), its in synergistic treatments, alongside DNA damage-inducing drugs, demonstrated anticancer potential for different acute leukemia subtypes (32,

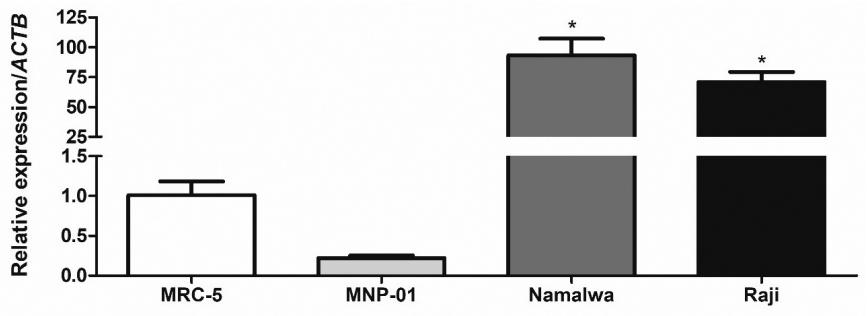

Figure 3. *Expression of poly-ADP-ribose polymerase 1 (PARP1) in Burkitt's lymphoma cell lines. Data are presented as mean±SD of three independent experiments. PARP1 gene expression was normalized by endogenous gene actin beta (ACTB). Expression in normal gastric cells MNP-01 and Namalwa and Raji cell lines derived from Burkitt's lymphoma was compared to that of lung fibroblasts MRC-5 using analysis of variance and multiple Bonferroni comparisons. *Significantly different from MRC-5 cells at p<0.0001.*

33), pointing to *PARP1* overexpression as a possible supportive pathway to malignancy.

Lastly, the two BKL cell lines presented some of the higher expression levels of *PARP1* in those analyzed. Immunoglobulin heavy locus/MYC proto-oncogene translocation is the most common mutation in BKL cells and, while it is related to overexpression of MYC transcription factor, it also seems to be responsible for down-regulation of *BRCA2* tumor-suppressor protein and accumulation of DNA double-strand breaks in these cells (34), which might explain *PARP1* overexpression as being a compensatory mechanism for perturbed DNA damage-repair pathways.

It is also relevant to note that, in accordance with the concept of synthetic lethality, the expression profile of BKL cells leads to them being sensitive to PARPi treatment as a total disruption of DNA damage-repair mechanisms induces apoptosis even in malignant cell phenotypes (34-36).

Conclusion

Overall, all malignant lineages in this study were found to overexpress PARP1. This observation is crucial for future studies exploring possible cellular oncogenic pathways and highlights the need for investigations into PARPi effectiveness against hematological disorders.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Machado CB, da Silva EL and Moreira-Nunes CA performed the study design; Machado CB and da Silva EL performed the cell culture analysis; Machado CB, da Silva EL and Nogueira BMD performed the molecular and statistical analysis; Machado CB, da Silva EL and Nogueira BMD, Moraes-Filho MO, Moraes MEA, Montenegro RC and Moreira-Nunes CA wrote the article. All Authors read and approved the final article.

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References

1 Ferreira D, Adega F and Chaves R: The importance of cancer cell lines as *in vitro* models in cancer methylome analysis and anticancer drugs testing. Oncogenomics and Cancer Proteomics – Novel Approaches in Biomarkers Discovery and Therapeutic Targets in Cancer, 2016. DOI: 10.5772/53110

2 Ben-David U, Beroukhim R and Golub TR: Genomic evolution of cancer models: perils and opportunities. Nat Rev Cancer *19(2)*: 97-109, 2019. PMID: 30578414. DOI: 10.1038/s41568-018-0095-3

3 Antoni D, Burckel H, Josset E and Noel G: Three-dimensional cell culture: a breakthrough in vivo. Int J Mol Sci *16(3)*: 5517-5527, 2015. PMID: 25768338. DOI: 10.3390/ijms16035517

4 Drexler HG and Quentmeier H: The LL-100 cell lines panel: tool for molecular leukemia-lymphoma research. Int J Mol Sci *21(16)*: 5800, 2020. PMID: 32823535. DOI: 10.3390/ijms21165800

5 Francica P and Rottenberg S: Mechanisms of PARP inhibitor resistance in cancer and insights into the DNA damage response. Genome Med *10(1)*: 101, 2018. PMID: 30593284. DOI: 10.1186/s13073-018-0612-8

6 McCann KE and Hurvitz SA: Advances in the use of PARP inhibitor therapy for breast cancer. Drugs Context *7*: 212540, 2018. PMID: 30116283. DOI: 10.7573/dic.212540

7 Li X, Li C, Jin J, Wang J, Huang J, Ma Z, Huang X, He X, Zhou Y, Xu Y, Yu M, Huang S, Yan X, Li F, Pan J, Wang Y, Yu Y and Jin J: High PARP-1 expression predicts poor survival in acute myeloid leukemia and PARP-1 inhibitor and SAHA-bendamustine hybrid inhibitor combination treatment synergistically enhances anti-tumor effects. EBioMedicine *38*: 47-56, 2018. PMID: 30472087. DOI: 10.1016/j.ebiom.2018.11.025

8 Schiewer MJ, Mandigo AC, Gordon N, Huang F, Gaur S, de Leeuw R, Zhao SG, Evans J, Han S, Parsons T, Birbe R, McCue P, McNair C, Chand SN, Cendon-Florez Y, Gallagher P, McCann JJ, Poudel Neupane N, Shafi AA, Dylgjeri E, Brand LJ, Visakorpi T, Raj GV, Lallas CD, Trabulsi EJ, Gomella LG, Dicker AP, Kelly WK, Leiby BE, Knudsen B, Feng FY and Knudsen KE: PARP-1 regulates DNA repair factor availability. EMBO Mol Med *10(12)*: e8816, 2018. PMID: 30467127. DOI: 10.15252/emmm.201708816

9 Sachdev E, Tabatabai R, Roy V, Rimel BJ and Mita MM: PARP inhibition in cancer: an update on clinical development. Target Oncol *14(6)*: 657-679, 2019. PMID: 31625002. DOI: 10.1007/s11523-019-00680-2

10 Kruk A, Ociepa T, Urasiński T, Grabarek J and Urasińska E: PARP-1 expression in CD34+ leukemic cells in childhood acute lymphoblastic leukemia: relation to response to initial therapy and other prognostic factors. Pol J Pathol *66(3)*: 239-245, 2015. PMID: 26619102. DOI: 10.5114/pjp.2015.54957

11 Lozzio CB and Lozzio BB: Human chronic myelogenous leukemia cell line with positive Philadelphia chromosome. Blood *45*: 321-334, 1975. PMID: 28157673. DOI: 10.1182/blood-2016-08-736025

12 Rumjanek VM, Trindade GS, Wagner-Souza K, de-Oliveira MC, Marques-Santos LF, Maia RC and Capella MA: Multidrug resistance in tumour cells: characterization of the multidrug resistant cell line K562-Lucena 1. An Acad Bras Cienc *73(1)*: 57-69, 2001. PMID: 11246270. DOI: 10.1590/s0001-37652001000100007

13 Rumjanek VM, Vidal RS and Maia RC: Multidrug resistance in chronic myeloid leukaemia: how much can we learn from MDR-CML cell lines? Biosci Rep *33(6)*: e00081, 2013. PMID: 24070327. DOI: 10.1042/BSR20130067

14 Fainstein E, Marcelle C, Rosner A, Canaani E, Gale RP, Dreazen O, Smith SD and Croce CM: A new fused transcript in Philadelphia chromosome positive acute lymphocytic leukaemia. Nature *330(6146)*: 386-388, 1987. PMID: 2825022. DOI: 10.1038/330386a0

15 Gillis S and Watson J: Biochemical and biological characterization of lymphocyte regulatory molecules. V. Identification of an interleukin 2-producing human leukemia T cell line. J Exp Med *152(6)*: 1709-1719, 1980. PMID: 6778951. DOI: 10.1084/jem.152.6.1709

16 Nyormoi O, Klein G, Adams A and Dombos L: Sensitivity to EBV superinfection and IUdR inducibility of hybrid cells formed between a sensitive and a relatively resistant Burkitt lymphoma cell line. Int J Cancer *12(2)*: 396-408, 1973. PMID: 4365093. DOI: 10.1002/ijc.2910120211

17 Epstein MA and Barr YM: Characteristics and mode of growth of tissue culture strain (EB1) of human lymphoblasts from Burkitt's lymphoma. J Natl Cancer Inst *34*: 231-240, 1965. PMID: 14293790. DOI: 10.1093/jnci/34.2.231

18 Jacobs JP, Jones CM and Baille JP: Characteristics of a human diploid cell designated MRC-5. Nature *227(5254)*: 168-170, 1970. PMID: 4316953. DOI: 10.1038/227168a0

19 Leal MF, Ribeiro HF, Rey JA, Pinto GR, Smith MC, Moreira-Nunes CA, Assumpção PP, Lamarão LM, Calcagno DQ, Montenegro RC and Burbano RR: YWHAE silencing induces cell proliferation, invasion and migration through the up-regulation of CDC25B and MYC in gastric cancer cells: new insights about YWHAE role in the tumor development and metastasis process. Oncotarget *7(51)*: 85393-85410, 2016. PMID: 27863420. DOI: 10.18632/oncotarget.13381

20 Bustin SA, Benes V, Garson JA, Hellemans J, Huggett J, Kubista M, Mueller R, Nolan T, Pfaffl MW, Shipley GL, Vandesompele J and Wittwer CT: The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments. Clin Chem *55(4)*: 611-622, 2009. PMID: 19246619. DOI: 10.1373/clinchem.2008.112797

21 Schmittgen TD and Livak KJ: Analyzing real-time PCR data by the comparative C(T) method. Nat Protoc *3(6)*: 1101-1108, 2008. PMID: 18546601. DOI: 10.1038/nprot.2008.73

22 Cruz M, Enes M, Pereira M, Dourado M and Sarmento Ribeiro AB: [Experimental models in oncology: contribution of cell culture on understanding the biology of cancer]. Rev Port Pneumol *15(4)*: 669-682, 2009. PMID: 19547898. DOI: 10.1016/s0873-2159(15)30163-x

23 Hynds RE, Vladimirou E and Janes SM: The secret lives of cancer cell lines. Dis Model Mech *11(11)*: dmm037366, 2018. PMID: 30459183. DOI: 10.1242/dmm.037366

24 Min A and Im SA: PARP inhibitors as therapeutics: beyond modulation of PARylation. Cancers (Basel) *12(2)*: 394, 2020. PMID: 32046300. DOI: 10.3390/cancers12020394

25 Faraoni I, Giansanti M, Voso MT, Lo-Coco F and Graziani G: Targeting ADP-ribosylation by PARP inhibitors in acute myeloid leukaemia and related disorders. Biochem Pharmacol *167*: 133-148, 2019. PMID: 31028744. DOI: 10.1016/j.bcp.2019.04.019

26 Moreira MA, Bagni C, de Pinho MB, Mac-Cormick TM, dos Santos Mota M, Pinto-Silva FE, Daflon-Yunes N and Rumjanek VM: Changes in gene expression profile in two multidrug resistant cell lines derived from a same drug sensitive cell line. Leuk Res *38(8)*: 983-987, 2014. PMID: 24996974. DOI: 10.1016/j.leukres.2014.06.001

27 Liu Y, Song H, Song H, Feng X, Zhou C and Huo Z: Targeting autophagy potentiates the anti-tumor effect of PARP inhibitor in pediatric chronic myeloid leukemia. AMB Express *9(1)*: 108, 2019. PMID: 31309361. DOI: 10.1186/s13568-019-0836-z

28 Hernández-Rodríguez M, Mendoza Sánchez PI, Macias Perez ME, Rosales Cruz E, Mera Jiménez E, Nicolás Vázquez MI and Miranda Ruvalcaba R: In vitro and computational studies showed that perezone inhibits PARP-1 and induces changes in the redox state of K562 cells. Arch Biochem Biophys *671*: 225-234, 2019. PMID: 31063714. DOI: 10.1016/j.abb.2019.05.002

29 Nieborowska-Skorska M, Maifrede S, Ye M, Toma M, Hewlett E, Gordon J, Le BV, Sliwinski T, Zhao H, Piwocka K, Valent P, Tulin AV, Childers W and Skorski T: Non-NAD-like PARP1 inhibitor enhanced synthetic lethal effect of NAD-like PARP inhibitors against BRCA1-deficient leukemia. Leuk Lymphoma *60(4)*: 1098-1101, 2019. PMID: 30277116. DOI: 10.1080/10428194.2018.1520988

30 Machado CB, DA Silva EL, DE Moraes Filho MO, DE Moraes MEA and Moreira-Nunes CA: PARP inhibitors as therapeutic options for tyrosine kinase-dependent leukemia: a review. Anticancer Res *40(6)*: 3055-3063, 2020. PMID: 32487599. DOI: 10.21873/anticanres.14286

31 Hegde M, Mantelingu K, Swarup H, Pavankumar C, Qamar I, Raghavan S and Rangappa K: Novel PARP inhibitors sensitize human leukemic cells in an endogenous PARP activity dependent manner. RSC Advances *6(8)*: 6308-6319, 2017. DOI: 10.1039/C5RA19150E

32 Falzacappa MV, Ronchini C, Faretta M, Iacobucci I, Di Rorà AG, Martinelli G, Meyer LH, Debatin KM, Orecchioni S, Bertolini F and Pelicci PG: The combination of the PARP

inhibitor rucaparib and 5FU is an effective strategy for treating acute leukemias. Mol Cancer Ther *14(4)*: 889-898, 2015. PMID: 25667168. DOI: 10.1158/1535-7163.MCT-14-0276

33 Garcia TB, Snedeker JC, Baturin D, Gardner L, Fosmire SP, Zhou C, Jordan CT, Venkataraman S, Vibhakar R and Porter CC: A small-molecule inhibitor of WEE1, AZD1775, synergizes with olaparib by impairing homologous recombination and enhancing DNA damage and apoptosis in acute leukemia. Mol Cancer Ther *16(10)*: 2058-2068, 2017. PMID: 28655785. DOI: 10.1158/1535-7163.MCT-16-0660

34 Maifrede S, Martin K, Podszywalow-Bartnicka P, Sullivan-Reed K, Langer SK, Nejati R, Dasgupta Y, Hulse M, Gritsyuk D, Nieborowska-Skorska M, Lupey-Green LN, Zhao H, Piwocka K, Wasik MA, Tempera I and Skorski T: IGH/MYC translocation associates with BRCA2 deficiency and synthetic lethality to PARP1 inhibitors. Mol Cancer Res *15(8)*: 967-972, 2017. PMID: 28634224. DOI: 10.1158/1541-7786.MCR-16-0468

35 Lord CJ and Ashworth A: PARP inhibitors: Synthetic lethality in the clinic. Science *355(6330)*: 1152-1158, 2017. PMID: 28302823. DOI: 10.1126/science.aam7344

36 Carrassa L, Colombo I, Damia G and Bertoni F: Targeting the DNA damage response for patients with lymphoma: Preclinical and clinical evidences. Cancer Treat Rev *90*: 102090, 2020. PMID: 32892059. DOI: 10.1016/j.ctrv.2020.102090

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