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Editorial

PARP Inhibitor in Ovarian Cancer Therapy

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Editorial

Ovarian cancer, the fifth leading cause in women malignancy and the second most commonly gynecological cancer, kills around 200,000 women per year in the world [1,2]. The overall five and ten year survival rate is only 30% and 10 %, respectively. Recent evidence suggests that poly (ADP-ribose) polymerase (PARP) inhibitors can specifically suppress BRCA1 mutation-induced ovarian tumors [3,4].

PARPs are a large family of 17 proteins encoded by different genes and sharing a conserved catalytic domain in humans [5]. Members of PARPs have been proved to participate in different cellular processes including chromatin structure modulation, nucleic acid metabolism, and apoptosis [5,6]. What attracts most attention is the function of PARPs in DNA damage response, especially in the repair of DNA single-strand breaks (SSBs) [7]. When SSBs occur, using NAD^+ as the substrate, active PARP catalyzes ADP-ribose covalently linked to the acceptor protein, forming the branched polymer of poly(ADP-ribose), namely PAR [8,9]. The polymer at DNA damage sites of SSBs recruits DNA ligase III, DNA polymerase ß, and XRCC1 protein to form base excision repair (BER) complex, which fixes DNA lesions of SSBs [7,10].

BRCA1 is a nuclear protein that suppress the tumorigenesis of breast and ovarian cancers [11]. Accumulated evidence suggests that BRCA1 is a core factor in homologous recombination (HR), a conserved mechanism to repair DNA double-strand breaks (DSBs) and maintain genomic stability [3,12]. As a result, loss of BRCA1 leads to breast and ovarian tumorigenesis [13]. Mechanically, BRCA1 interacts with the downstream partner PALB2 at DNA lesions. This interaction promotes the recruitment of BRCA2 and RAD51 to the site of DNA damage, which achieves the repair of DSBs [14-16].

Based on the above, PARP inhibitors are developed for treating the BRCA1-related ovarian cancer by a strategy of synthetic lethality [17]. In brief, a large number of SSBs are induced daily by various types of environmental and internal hazards in cells [18]. PARP inhibitors block SSBs repair pathway by inhibiting PAR synthesis. Accumulated SSBs will be converted to DSBs during DNA replication or when two SSBs locate closely. These DSBs could be repaired by HR in BRCA1 proficient cells. However, in tumor cells bearing BRCA1 mutations, deficient HR leads to a failure of DSBs repair and induces cell death [4,19].

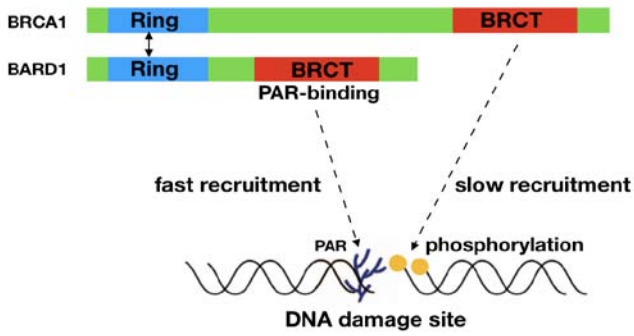

Figure 1:

But how to explain that PAPR inhibitors are only effective for around 40% BRCA1 mutation tumors [20]? Besides SSBs repair, poly (ADP-ribosylation) is recently found to have an important function in BRCA1 regulated-HR [21,22]. BRCA1 contains an N' Ring domain and a C' BRCT domain [22,23]. The C' BRCT targets BRCA1 slowly to DNA damage sites, while PAR mediates the fast recruitment of BRCA1 by the interaction between PAR and the BRCA1/BARD1 complex, linked by their Ring domains [24,25] (Figure 1). Inhibition of PAR synthesis by PARP inhibitor completely blocks the recruitment of BRCA1 to DNA damage sites in cells bearing BRCT mutations, and thus abolishes HR. However, a set of cancer-associated mutations exist in the Ring domain of BRCA1. In these cases, the loss of PAR does not change the behavior of BRCA1 since the fast recruitment pathway of BRCA1 is originally defective regardless the presence of PAR. BRCA1 could be targeted slowly to DNA damage sites by the slow recruitment by the BRCT domain. PARP inhibitors, therefore, do not selectively kill tumor cells with these mutations. Thus, we propose that cancer cells with BRCA1-BRCT mutations would be hypersensitive to PARP inhibitor, and the chemotherapy of PARP inhibitor drugs may be applied to ovarian cancer patients bearing these mutations.

References

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015; 1: 505-27.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics. CA Cancer J Clin. 2017. 67: 7-30.
3. Huen MS, Sy SM, Chen J. BRCA1 and its toolbox for the maintenance of genome integrity. Nat Rev Mol Cell Biol. 2010; 11: 138-148.
4. Sonnenblick A, de Azambuja E, Azim HA Jr, Piccart M. An update on PARP inhibitors--moving to the adjuvant setting. Nat Rev Clin Oncol. 2015; 12: 27-41.
5. Ame JC, Spenlehauer C, de Murcia G. The PARP superfamily. Bioessays. 2004. 26: 882-893.
6. Morales J, Li L, Fattah FJ, Dong Y, Bey EA, Patel M. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. Crit Rev Eukaryot Gene Expr. 2014; 24: 15-28.
7. De Vos M, Schreiber V, Dantzer F. The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art. Biochem Pharmacol.

2012; 84: 137-146.

8. Kim MY, Zhang T, Kraus WL. Poly(ADP-ribosyl)ation by PARP-1: 'PAR-laying' NAD+ into a nuclear signal. Genes Dev. 2005; 19: 1951-1967.

9. Luo X, Kraus WL. On PAR with PARP: cellular stress signaling through poly(ADP-ribose) and PARP-1. Genes Dev. 2012; 26: 417-432.

10. Caldecott KW, Aoufouchi S, Johnson P, Shall S. XRCC1 polypeptide interacts with DNA polymerase beta and possibly poly (ADP-ribose) polymerase, and DNA ligase III is a novel molecular 'nick-sensor' in vitro. Nucleic Acids Res. 1996. 24: 4387-4394.

11. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994; 266: 66-71.

12. Drew Y. The development of PARP inhibitors in ovarian cancer: from bench to bedside. Br J Cancer. 2015; 113: S3-9.

13. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016; 16: 110-120.

14. Westermark UK, Reyngold M, Olshen AB, Baer R, Jasin M, Moynahan ME, et al. BARD1 participates with BRCA1 in homology-directed repair of chromosome breaks. Mol Cell Biol. 2003; 23: 7926-7936.

15. SM Sy, Huen MS, Chen J. PALB2 is an integral component of the BRCA complex required for homologous recombination repair. Proc Natl Acad Sci U S A. 2009; 106: 7155-7160.

16. Zhang F, Ma J, Wu J, Ye L, Cai H, Xia B, et al. PALB2 links BRCA1 and BRCA2 in the DNA-damage response. Curr Biol. 2009; 19: 524-529.

17. De Lorenzo SB, Patel AG, Hurley RM, Kaufmann SH. The Elephant and the Blind Men: Making Sense of PARP Inhibitors in Homologous Recombination Deficient Tumor Cells. Front Oncol. 2013; 3: 228.

18. Ciccia A, Elledge SJ. The DNA damage response: making it safe to play with knives. Mol Cell. 2010; 40: 179-204.

19. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005; 434: 917-921.

20. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet. 2010; 376: 245-251.

21. Li M, Lu LY, Yang CY, Wang S, Yu X. The FHA and BRCT domains recognize ADP-ribosylation during DNA damage response. Genes Dev. 2013; 27: 1752-1768.

22. Li M, Yu X. Function of BRCA1 in the DNA damage response is mediated by ADP-ribosylation. Cancer Cell. 2013; 23: 693-704.

23. Baer R. Luring BRCA1 to the scene of the crime. Cancer Cell. 2013; 23: 565-567.

24. Wu LC, Wang ZW, Tsan JT, Spillman MA, Phung A, Xu XL, et al. Identification of a RING protein that can interact in vivo with the BRCA1 gene product. Nat Genet. 1996. 14: 430-440.

25. Brzovic PS, Rajagopal P, Hoyt DW, King MC, Klevit RE. Structure of a BRCA1-BARD1 heterodimeric RING-RING complex. Nat Struct Biol. 2001; 8: 833-837.

26. Liu JF, Konstantinopoulos PA, Matulonis UA. PARP inhibitors in ovarian cancer: current status and future promise. Gynecol Oncol. 2014; 133: 362-369.

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