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PARP inhibitors potentiate chemotherapy of NET cells and tumors and PAPR1-knockdown suppresses growth of NET tumors in mice#

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BACKGROUND

In mammalian cells, poly(ADP-ribose) polymerase-1 (PARP1) is among the earliest proteins to reach the site of DNA damage and play key roles in different cellular responses ranging from DNA repair to cell death. PARP-inhibitors are recommended in mono or combination therapy for a subset of breast and ovarian cancers with BRCAness type of DNA repair deficiency. In addition, current clinical trials are examining whether PARP-inhibitors can potentiate the efficacy of chemotherapy or peptide receptor radionuclide therapy. Here, using in vitro and mouse models of human-derived NET cells we examined the mechanism by which targeting PARP1-targeting could influence the growth of NET tumors and their response to chemotherapy.

METHODS

We used orthotopic liver tumor model in BALB/c nude mice using human pancreatic carcinoid-derived BON-1 cells that stably express luciferase gene that facilitates bioluminescence imaging of tumors. To examine the role of PARP1 per se in the growth of tumors, we compared the growth of tumors of PARP1-wild type and PARP1 knock-down (shRNA approach) BON-1 cells. We also examined the growth suppressive effect of PARP-inhibitor on the response of PARP1-wt cells to chemotherapy (temozolomide and streptozotocin) using the cellular and mouse models. The growth and therapeutic responses in these models were monitored by bioluminescence in vivo and by various biochemical, immunohistological and transcriptomic analyses of cells or tumors after sacrifice.

RESULTS

We observed that the treatment with chemotherapeutic agents rapidly activated PARP1 in NET cells and tumors, and PARP inhibitors efficiently blocked this activation. PARP-inhibition increased the cytocidal effect of drugs via suppression of growth and increased cell death due to unrepaired DNA damage in both cellular and tumor models. In the mouse model of liver tumors, a cytostatic dose regime of temozolomide became significantly cytocidal with tumor shrinkage when combined with PARP-inhibitor. Interestingly, we observed that the PARP1 depletion per se suppressed the growth of tumors, although there is no known DNA repair-defect in these cells. The analyses of tumors revealed that PARP1-knckdown decreased Ki67 proliferative index accompanied by alterations in key cell cycle-related genes that control cell growth, increased expression of E-cadherin and increased expression of cell death related genes.

CONCLUSIONS

Our results indicate that PARP-inhibition can be a promising strategy for not only potentiating the efficacy of chemotherapy but also for a maintenance therapy to restrict growth of NETs before, during and after chemotherapy.

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