STING AGONISM OVERCOMES STAT3-MEDIATED IMMUNOSUPPRESSION AND ADAPTIVE RESISTANCE TO PARP INHIBITION IN OVARIAN CANCER

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Background PARP inhibition (PARPi) has demonstrated potent therapeutic efficacy in patients with BRCA-mutant ovarian cancer. However, acquired resistance to PARPi remains a major challenge in the clinic. PARPi-resistant ovarian cancer mouse models were generated by long-term treatment of olaparib in syngeneic Brca1-deficient ovarian tumors. STAT3-mediated immunosuppression was investigated in vitro by co-culture experiments and in vivo by analysis of immune cells in the TME of human and mouse PARPi-resistant tumors. Whole genome transcriptome analysis was performed to assess the anti-tumor immunomodulatory effect of STING (stimulator of interferon genes) agonists on myeloid cells in the TME of PARPi-resistant ovarian tumors. A STING agonist was used to overcome STAT3-mediated immunosuppression and acquired PARPi resistance in syngeneic and PDX models of ovarian cancer.

Methods In this study, we uncover an adaptive resistance mechanism to PARP inhibition mediated by tumor associated macrophages (TAMs) in the tumor microenvironment (TME). Markedly increased populations of pro-tumor macrophages are found in BRCA-deficient ovarian tumors that rendered resistance to PARPi in both murine models and patients. Mechanistically, PARPi inhibition elevates the STAT3 signaling pathway in tumor cells, which in turn promotes pro-tumor polarization of TAMs. STAT3 ablation in tumor cells mitigates polarization of pro-tumor macrophages and increases tumor infiltrating T-cells upon PARP inhibition. These findings are corroborated in patient-derived, PARPi-resistant BRCA1-mutant ovarian tumors. Importantly, STING agonists reshape the immunosuppressive TME by reprogramming myeloid cells and overcome the TME-dependent adaptive resistance to PARPi in ovarian cancer. This effect is further enhanced by addition of PD-1 blockade.

Results In this study, we uncover an adaptive resistance mechanism to PARP inhibition mediated by tumor associated macrophages (TAMs) in the tumor microenvironment (TME). Markedly increased populations of pro-tumor macrophages are found in BRCA-deficient ovarian tumors that rendered resistance to PARPi in both murine models and patients. Mechanistically, PARPi inhibition elevates the STAT3 signaling pathway in tumor cells, which in turn promotes pro-tumor polarization of TAMs. STAT3 ablation in tumor cells mitigates polarization of pro-tumor macrophages and increases tumor infiltrating T-cells upon PARP inhibition. These findings are corroborated in patient-derived, PARPi-resistant BRCA1-mutant ovarian tumors. Importantly, STING agonists reshape the immunosuppressive TME by reprogramming myeloid cells and overcome the TME-dependent adaptive resistance to PARPi in ovarian cancer. This effect is further enhanced by addition of PD-1 blockade.

Conclusions We elucidate an adaptive immunosuppression mechanism rendering resistance to PARP in BRCA1-mutant ovarian tumors. This is mediated by enrichment of pro-tumor TAMs propagated by PARP-induced STAT3 activation in tumor cells. We also provide a new strategy to reshape the immunosuppressive TME with STING agonist and overcome acquired PARPi resistance in ovarian cancer (figure 1).

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REFERENCES

Abstract 910 Figure 1 Graphical Abstract Overcoming TME-dependent adaptive resistance to PARPi in BRCA1-deficient ovarian cancer with STING agonist treatment. Over a course of PARPi treatment, BRCA1-deficient ovarian tumors develop TME-dependent or -independent adaptive resistance to PARPi therapy. PARPi induces STAT3 signaling in the tumor cells, which in turn polarizes macrophages towards pro-tumor M2-like TAMs and contributes to TME-dependent PARPi resistance in ovarian cancer. Treatment with a STING agonist can reshape the immunosuppressive TME to an anti-tumor status by reprogramming myeloid cells, re-sensitizing the resistant tumors to PARPi therapy in BRCA1-deficient ovarian cancer.