Abstracts

TARGETING LIPID METABOLISM TO IMPROVE PARP INHIBITOR RESPONSE IN BRCA-ASSOCIATED TNBC

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Background Poly (ADP-ribose) polymerase inhibitor (PARPi) therapy induces DNA damage in tumors to activate cGAS/STING signaling, increasing tumor antigens and immune infiltration. The full response to PARPi requires intact T-cell responses, demonstrating a previously unappreciated role for tumor-immune interactions. However, we found that tumor-associated macrophages (TAMs) suppress T-cell function in response to PARPi and enhance lipid synthesis to exert their suppressive effect. Despite the lipogenic transformation of TAMs, the metabolic landscape of tumors and immune infiltrates in BRCA-deficient TNBC as well as their impact on therapeutic responses, remain poorly understood.

Methods We performed single-cell analysis of pretreatment human TNBC with or without BRCA mutations to determine the transcriptional metabolic landscape. To study the immunometabolic effect of PARPi we used the K14-Cre/Brca1(+/−)/p53(−/−) model. Tumor-bearing mice were treated with vehicle or PARPi (Olaparib) for 5 days. We performed gene expression profiling, glucose (2NBDG) and lipid (BODIPY-C16) uptake analysis by flow cytometry, and mass spectrometry-based metabolome analysis to determine the metabolic profile of tumors. To inhibit lipid metabolic TAMs mice were treated with fatostatin or anti-CSF1-R.

Results Our single-cell analysis revealed that TNBC epithelial cells with BRCA mutations exhibit increased expression of genes associated with fatty acid metabolism and adipogenesis compared to BRCA-WT cells. Using murine model, we observed that PARPi therapy induces an influx of macrophage and CD8+ T cells. However, this change was accompanied by an upregulation of genes linked to lipid and fatty acid metabolic processes. Tumors in vehicle treated mice took up more glucose (2NBDG) and lipids (BODIPY-C16) than immune cells. However, PARPi treatment mitigated the difference between tumor cells and immune cells. Notably, macrophages were the predominant immune cell that showed increased glucose and lipid uptake. Importantly, these macrophages expressed PD-L1 and CSF1-R, and PARPi treatment significantly increased their population. Furthermore, ex vivo macrophages differentiated in the presence of PARPi exhibited gene signature profiles associated with lipid metabolism, suggesting a direct role of PARPi in regulating macrophage metabolism to induce a suppressive phenotype. The metabolite analysis demonstrated that PARPi treatment increased lipid levels in the tumor microenvironment (TME). Interestingly, this effect was prevented in mice treated with anti-CSF1-R. Finally, inhibiting lipid metabolism with fatostatin in combination with PARPi and anti-CSF1-R exhibited unparalleled durability in tumor response.

Conclusions We demonstrated that PARPi remodels the immunometabolic landscape of BRCA tumors, promoting an accumulation of lipids and lipid-loaded macrophages within the TME, which ultimately abrogate the antitumor immune response and compromise the efficacy of PARPi.

Ethics Approval The present study was approved by BWH CMM IACUC, protocol number is 2020N000142.

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