Platinoid-chemotherapy upregulation of MHC-I machinery in tumor cells determines the response to checkpoint inhibitors

Ingmar Niels Bastian[1], Weihua Li[1], Kathleen Fisch[2], Michael Karin[1*], **Shabnam Shalapour[1*]**

[1] Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology, School of Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093
[2] Center for Computational Biology & Bioinformatics, Department of Medicine, University of California, San Diego, La Jolla, California, US
[*] Co-last author

Background

Immune checkpoint therapy (ICT) has the potential to radically transform cancer treatment using antibodies that target inhibitors of T cell activation, such as PD-1 and CTLA4. However, even in metastatic melanoma and non-small cell lung cancer (NSCLC), malignancies that are highly ICT responsive, response rates rarely exceed 40%. Furthermore, many common malignances, including prostate (PCa) and pancreatic (PanCa) cancers, are ICT refractory. Causes of treatment failure are largely unknown. Early work correlated ICT responsiveness across different tumor types with mutational burden, which presumably accounts for expression of new tumor antigens that can be recognized by cytotoxic T lymphocytes (CTL). Although this correlation may hold for a single tumor type, several malignances initially predicted to be non-responsive based on low mutational burdens, e.g. renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC), are almost as responsive to PD-1 inhibitors as highly mutated NSCLC. Clearly, factors other than mutational burden are of importance. LOF mutations in the IFNγ signaling pathway also confer ICT resistance. We aim to study the factors that affect the response to ICT in prostate cancer.

Methods

Using the autochthonous transgenic adenocarcinoma of the mouse prostate (TRAMP) model of metastatic PCa and subcutaneous transplantation of mouse Myc-CaP (MC) and Ovalbumin (Ova)-expressing newly developed PCa cell lines, we examined how low-dose chemotherapy can potentiate ICT. We also conducted proteomic, transcriptomic, and ATAC-seq analyses of cancer cells treated with Oxaliplatin or Cisplatin to understand the underlying mechanism of the immunogenic activity of low dose Oxaliplatin. Additionally, we used CRISPR-Cas9 genome editing to ablate a select few genes found to be induced by Oxaliplatin and/or Cisplatin treatment through RNA-seq and ATAC-seq analyses: IRF-1, STAT1, and IFNγR2.

Results

HCC responds to PD-1 blockade, but PCa does not, despite low mutational burden. RNA-seq analysis revealed that, unlike HCC, PCa cells poorly express MHC-I molecules and components of the MHC-I antigen processing and presentation machinery. We found that treatment of PCa cells and other tumor types with platin-based drugs, especially low dose Oxaliplatin, led to a pronounced upregulation of MHC-I molecules and their antigen generating and loading machinery. Most importantly, Oxaliplatin synergistically potentiated the effect of exogenous IFNγ; a conclusion based on two cumulative observations. First, ATAC-seq analyses revealed that Oxaliplatin activates MHC machinery through different pathways compared to well-known IFNγ signaling. Second, Oxaliplatin upregulates IFNγR2 expression in cancer cells. Induction of IFNγR2, which was needed for Oxaliplatin-potentiation of ICT-induced tumor rejection in vivo, depended on NF-κB signaling.

Conclusion

Our data indicates that combining ICT with an appropriate low dose platinoid chemotherapeutic agent is useful in reinvigorating the immune response to tumors that have escaped immune destruction due to MHC-I downregulation and do not respond to single agent therapy.
The authors declare no competing financial interests.

Research was supported by NIH (PO1, CA127923 and AI043477), and fellowships from Irvington-Cancer research Institute and PCF YI award (to S.S). M.K. is an American Cancer Society Research Professor and holds the Ben and Wanda Hildyard Chair for Mitochondrial and Metabolic Diseases.