POSTER PRESENTATION

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Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells

Kibem Kim^{1*}, Andrew Skora², Zhaobo Li², Ada Tam³, Luis Diaz², Nickolas Papadopoulos², Lee Blosser³, Kenneth Kinzler², Bert Vogelstein², Shibin Zhou²

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Recent clinical trials have shown highly promising responses in a subset of patients treated with immune checkpoint inhibitory anti-programmed cell death-1, anti-programmed cell death ligand-1 (PD-1), and anti-cytotoxic T-lymphocyte-associated antigen-4 antibodies (CTLA-4) [1-4]. However, immunotherapy against poorly immunogenic cancers remains a challenge. Large, modestly immunogenic CT26 tumors or poorly immunogenic metastatic 4T1 tumors in mice were unresponsive to anti-PD-1 and anti-CTLA-4 treatments. Co-treatment with DNA methyltransferase and HDAC inhibitors, and checkpoint inhibitors markedly improved treatment outcomes, curing more than 80% of the tumor-bearing mice. Functional studies revealed that the primary targets of the epigenetic modulators were myeloid-derived suppressor cells (MDSCs). In addition, reduction of MDSCs using antibodies directed against them or a PI3K inhibitor that reduced circulating MDSCs had similar antitumor effects to those observed with the epigenetic modulators. Our results show that elevated myeloid-derived suppressor cells (MDSCs) are responsible for the resistance to checkpoint inhibitors and that elimination of MDSCs can lead to cures of experimental, metastatic tumors.

Authors' details

¹Medical Scientist Training Program, Ludwig Center for Cancer Genetics and Therapeutics, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA. ²Ludwig Center for Cancer Genetics and Therapeutics, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.

³Medical Scientist Training Program, Ludwig Center for Cancer Genetics and Therapeutics, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
Full list of author information is available at the end of the article

USA. ³Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.

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