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Indoleamine 2,3-dioxygenase 1 inhibition targets anti-PD1-resistant lung tumors by blocking myeloid-derived suppressor cells

Ailin Li, Hampartsoum B. Barsoumian, Jonathan E. Schoenhals, Taylor R. Cushman, Mauricio S. Caetano, Xiaohong Wang, David R. Valdecanas, Sharareh Niknam, Ahmed I. Younes, Guang Li, Wendy A. Woodward, Maria Angelica Cortez, James W. Welsh

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Abstract

Indoleamine 2,3-dioxygenase 1 (IDO1), involved in the catabolism of tryptophan (Trp) to kynurenine (Kyn) is an important regulator of tumor-mediated immunosuppression implicated in resistance to anti-PD1 immunotherapy. We investigated the role of IDO1 in an anti-PD1-resistant lung cancer model (344SQ_R) compared to the parental 344SQ tumors (344SQ_P). IDO1 was overexpressed in tumor-infiltrating leukocytes, and plasma Kyn levels were increased, in 344SQ_R vs. 344SQ_P. The IDO1 inhibitor INCB023843 retarded tumor growth and reduced lung metastases in 344SQ_R. IDO1 was expressed at higher levels in $F4/80^{+}Gr1^{int}CD11b^{+}$ myeloid-derived suppressor cells (MDSCs) that were prominent in 344SQ_R. The INCB023843 reduced IDO1 expression and percentages of these MDSCs while increasing $CD8^{+}$ T cells infiltration, hence reactivating antitumor T-cell responses in 344SQ_R. Therefore, IDO1 inhibition holds promise for treating lung cancer that does not respond to anti-PD1 therapy.

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