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Interleukin-1α mediates resistance to immunotherapy in melanoma

Manisha Singh and Shubhra Singh, Zhilan Xiao, Karishma Bavisi, Jason Roszik, Brenda D. Melendez, Zhiqiang Wang, Mark J. Cantwell, Richard E. Davis, Greg Lizee, Patrick Hwu, Sattva S. Neelapu, Willem W. Overwijk

The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA

Currently, immunotherapies are the most promising treatments for metastatic melanoma. However, most patients with melanoma do not respond or only partially respond to available immunotherapies. Results of preclinical and clinical studies suggest that both innate and acquired resistance play roles in melanoma resistance to immunotherapy. Identifying the factors and mechanisms involved in this resistance could help us design new strategies to avoid resistance and improve therapeutic efficacy.

Inflammation has long been associated with cancer initiation and progression; however, how inflammation causes immune suppression in the tumor microenvironment and resistance to immunotherapy is not well understood. Here, we show that both innate proinflammatory cytokine interleukin-1α (IL-1α) and immunotherapy-induced IL-1α make melanoma resistance to immunotherapy. In a mouse melanoma model, we found that tumor size was inversely correlated with response to immunotherapy. Large tumors had higher levels of IL-1α, Th2 cytokines, polymorphonuclear (PMN)-MDSCs, and regulatory T cells but lower levels of IL-12, Th1 cytokines, and activated CD4+ and CD8+ T cells. We found that therapy with rAd.CD40L (adenovirus-encoded CD40 ligand) increased tumor levels of IL-1α and polymorphonuclear (PMN)-MDSCs. Blocking the IL-1 signaling pathway significantly decreased rAd.CD40L-induced polymorphonuclear (PMN)-MDSCs and their associated PD-L1 expression in the tumor microenvironment and enhanced tumor-specific immunity. Similarly, blocking the IL-1 signaling pathway improved the anti-melanoma activity of anti-PD-L1 antibody therapy. Our study suggests that blocking the IL-1α signaling pathway may increase the efficacy of immunotherapies against melanoma.

msingh4@mdanderson.org