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# Abstract

Cutaneous melanomas express a high number of potential neoepitopes, yet a substantial fraction of melanomas shift into immunologically cold phenotypes. Using cellular systems, mouse models and large datasets, we identify the tumor-secreted growth factor midkine (MDK) as a multilayered inhibitor of antigen-presenting cells. Mechanistically, MDK acts systemically in primary tumors, lymph nodes and the bone marrow, promoting a STAT3-mediated impairment of differentiation, activation and function of dendritic cells (DCs), particularly, conventional type 1 DCs (cDC1s). Furthermore, MDK rewires DCs toward a tolerogenic state, impairing $CD8^+$ T cell activation. Downregulating MDK improves DC-targeted vaccination, CD40 agonist treatment and immune checkpoint blockade in mouse models. Moreover, we present an MDK-associated signature in DCs that defines poor prognosis and immune checkpoint blockade resistance in individuals with cancer. An inverse correlation between MDK- and cDC1-associated signatures was observed in a variety of tumor types, broadening the therapeutic implications of MDK in immune-refractory malignancies.