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Melanoma-secreted factor MIDKINE drives immune checkpoint blockade resistance and predicts clinical outcome

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Cutaneous melanoma is the most lethal form of skin cancer, characterized by a high metastatic potential and a remarkable ability to evade immune surveillance. Therapies aimed at the deactivation of intrinsic mechanisms of immunosuppression have improved clinical response rates, but about 40-50% of patients still succumb to metastatic disease. Primary resistance to immunotherapy is often observed in patients with either low immunogenic tumors (cold tumors), or with lesions infiltrated with immune suppressive cells, such as tumor-associated macrophages (TAMs), T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Yet, mechanisms that define tumor immunogenicity, and more importantly, biomarkers to predict clinical responses in patients, are still pending needs in the field. We have previously identified a melanoma-secreted protein, called MIDKINE (MDK), with critical roles in lymphangiogenesis and metastasis. We have now identified a new MDK-related transcriptomic gene signature with a high significant correlation to survival in melanoma and other tumor types. This MDK-associated signature was found correlated to increased immune cell infiltration, in particular, of MDSCs and Tregs. Mechanistically, we assigned this immunomodulatory function of MDK to a secretory program acting both on tumor cells (via ALK) and on myeloid cells (associated to immunossupressive roles of STAT3). Gain-of-function assays demonstrated that MDK blunts the response to immune checkpoint blockers actively pursued in the clinic. The physiological impact of these results was further strengthened by finding that MDK expression predicts resistance to anti-PD1-based treatment in two independent cohorts of melanoma patients. These results provide insight on long-pursued mechanisms of tumor-immune evasion in melanoma, and uncovered MDK as a tractable biomarker for the response to clinically relevant immunomodulatory agents.

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