MEDICAL THERAPIES AND PHARMACOLOGY

DC-HIL IS A NOVEL IMMUNE CHECKPOINT AND A PROMISING TARGET FOR TREATING MELANOMA AND OTHER CANCERS

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Introduction: Despite the success of immune checkpoint blockers (like anti-PD1/PDL1 mAb) in improving survival of patients with melanoma and other cancers, most cases fail to benefit from this current best-treatment option.

Objective: To develop better immunotherapy for melanoma and other cancers.

Materials & Methods: DNA subtraction analyses; Knock out mice; In vitro cell assays; mAb production.

Results: We discovered DC-HIL (also known as Gpnmb), which exists in 2 forms: a cell-bound receptor, and a soluble factor secreted into circulation. We have shown DC-HIL to inhibit T-cell activation by binding to its ligand syndecan-4 on effector T cells. In healthy individuals, we showed DC-HIL expressed by some immune cells at very low levels. By contrast, in patients with melanoma and other cancers (including breast, colorectal, kidney, lung, prostate), DC-HIL is expressed highly by myeloid-derived suppressor cells (MDSC) that expand exponentially with progression of the malignancy. Soluble DC-HIL (sDC-HIL) is also detectable in the blood of many of these patients at levels increasing with metastasis. MDSC are the most powerful suppressors of T-cell activation, and we showed the DC-HIL receptor on MDSC to mediate this adverse function. We have generated an anti-DC-HIL mAb that in animal models can reduce melanoma growth and metastasis dramatically, as well as block the T-cell suppressor function of MDSC from patients with metastatic melanoma and other cancers.

Conclusions: We identified a novel immune checkpoint molecule with great promise as a therapeutic target for melanoma and other cancers.