A NOVEL ANTIBODY TARGETING HUMAN MONOCYTE-INTRINSIC PD-L1 PROMOTES IMMUNE STIMULATORY FUNCTIONS OF MONOCYTES FOR ANTITUMOR IMMUNITY

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Background. Current PD-L1 targeting antibodies have been developed to block PD-L1’s interaction with PD-1, thereby preventing inhibition of T cell cytotoxicity. However, there has been limited clinical success in the treatment of cancers, despite high expression of PD-L1. Recent reports have demonstrated that tumor-intrinsic PD-L1 can signal intracellularly to promote cell survival independent of PD-1 ligation, potentially explaining why some cancer patients do not respond to immune checkpoint therapies. Besides tumor cells, host myeloid cells are sources of PD-L1 and can be highly immunosuppressive. Unfortunately, the intrinsic functions of PD-L1 in myeloid cells has not been well studied. We aim to dissect the intrinsic signaling of PD-L1 in monocytes, a subset of myeloid cells, and to investigate how this may be impairing antitumor immunity.

Methods. Our lab has identified a new PD-L1 antibody (clone H1A), which destabilizes PD-L1 at the cell surface and induces its degradation. In our experiments, we used human PBMCs isolated from healthy donor blood and isolated monocytes from PBMCs using negative magnetic selection. To study the effects H1A-induced PD-L1 degradation on human monocytes, we assessed monocyte phenotype, function, and transcriptional profile by flow cytometry, immunoassays, and single-cell RNA sequencing, respectively. To study the indirect effects of H1A on T cell functional states, we evaluated PBMCs by flow cytometry and mass cytometry using T cell focused panels. To evaluate T cell function, we used cytotoxic killing assays.

Results. H1A-treated monocytes resulted in decreased total expression of PD-L1 and a transient increase of CCL2 secretion across multiple donors. H1A treated monocytes had greater polyfunctionality based on the number of analytes secreted by single cells. H1A treated monocytes had significant transcriptional profile changes, related to transcriptional activation of CCL2. PBMCs treated with H1A resulted in more effector CD8 T cell and less regulatory T cell populations. Finally, H1A treatment of PBMCs resulted in greater T cell-mediated killing of tumor cells.

Conclusions. Our data suggests monocyte-intrinsic PD-L1 signaling inhibits transcriptional activation and subsequent secretion of CCL2 in human monocytes, thereby restricting effector T cells populations. H1A antibody abolishes this inhibitory mechanism and restores effector T cell responses. The significance of our studies contributes to understanding a new mechanism of action of PD-L1 in monocytes that may cause cancer patients to not respond to anti-PD-1/PD-L1 therapy. The H1A antibody provides a new tool that can overcome these limitations to enhance T-cell mediated antitumor immunity and prolong survival of patients with lethal cancers.

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