Focus on: Immuno-Oncology

Articles from the journal Science Translational Medicine

PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations

Abstract: PD-L1 and PD-1 (PD) pathway blockade is a highly promising therapy and has elicited durable antitumor responses and long-term remissions in a subset of patients with a broad spectrum of cancers. How to improve, widen, and predict the clinical response to anti-PD therapy is a central theme in the field of cancer immunology and immunotherapy. Oncologic,
immunologic, genetic, and biological studies focused on the human cancer microenvironment have yielded substantial insight into this issue. Here, we focus on tumor microenvironment and evaluate several potential therapeutic response markers including the PD-L1 and PD-1 expression pattern, genetic mutations within cancer cells and neoantigens, cancer epigenetics and effector T cell landscape, and microbiota. We further clarify the mechanisms of action of these markers and their roles in shaping, being shaped, and/or predicting therapeutic responses. We also discuss a variety of combinations with PD pathway blockade and their scientific rationales for cancer treatment. Full text...

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**The PDL1-PD1 Axis Converts Human TH1 Cells into Regulatory T Cells**

**Abstract**: Immune surveillance by T helper type 1 (TH1) cells is not only critical for the host response to tumors and infection, but also contributes to autoimmunity and graft-versus-host disease (GVHD) after transplantation. The inhibitory molecule programmed
death ligand 1 (PDL1) has been shown to anergize human TH1 cells, but other mechanisms of PDL1-mediated TH1 inhibition such as the conversion of TH1 cells to a regulatory phenotype have not been well characterized. We hypothesized that PDL1 may cause TH1 cells to manifest differentiation plasticity. Conventional T cells or irradiated K562 myeloid tumor cells overexpressing PDL1 converted TBET+ TH1 cells into FOXP3+ regulatory T (Treg) cells in vivo, thereby preventing human-into-mouse xenogeneic GVHD (xGVHD). Either blocking PD1 expression on TH1 cells by small interfering RNA targeting or abrogation of PD1 signaling by SHP1/2 pharmacologic inhibition stabilized TH1 cell differentiation during PDL1 challenge and restored the capacity of TH1 cells to mediate lethal xGVHD. PD1 signaling therefore induces human TH1 cells to manifest in vivo plasticity, resulting in a Treg phenotype that severely impairs cell-mediated immunity. Converting human TH1 cells to a regulatory phenotype with PD1 signaling provides a potential way to block GVHD after transplantation. Moreover, because this conversion can be prevented by blocking PD1 expression or pharmacologically inhibiting SHP1/2, this pathway provides a new therapeutic direction for enhancing T cell immunity to cancer and infection. Full text...

**LIGHTing up the tumor microenvironment**

*Article from the journal Science Signaling*

**Abstract**: Immune cells can recognize and attack tumor cells. However, various aspects of a tumor interfere with this response. Two studies have found ways to potentially overcome these barriers. Antibodies blocking the suppressive T cell checkpoint interaction between programmed cell death protein 1 (PD-1) on T cells and its ligand (PD-L1) on tumor cells (anti-PD-L1 therapy) is effective in some patients but often requires combination with other checkpoint-targeted therapies to increase its efficacy and, still, some tumors are unresponsive. Tang et al. found that the amount of T cell infiltration, but not PD-L1 abundance, determined the response of tumors to anti-PD-L1 therapy. To increase lymphocyte infiltration in therapy-resistant tumors, the authors designed antibodies that fused LIGHT, a ligand for the lymphotoxin ?? receptor (L??TR) on stroma cells, to an antibody against a protein on the surface of tumor cells [in this case, epidermal growth factor receptor (EGFR)]. LIGHT-fusion antibodies stimulated the abundance of inflammatory cytokines in tumor homogenates, and this positively correlated with increased abundance of infiltrating lymphocytes. However, the LIGHT-fusion antibody also increased the abundance of PD-L1 on the tumor cell surface, making it ineffective as a single-agent therapy. Combining the LIGHT-fusion antibody with the PD-L1 antibody
eradicated established mouse and human tumors in immune-competent or immune-
reconstituted mice, respectively, and enabled mice to reject subsequently injected tumor
cells. Full text...

*Science* Technology Feature

**Diving deep into cell signaling**

New proteomics tools enable researchers to dive deeply into signaling networks, allowing
them to tease out interactions among key molecules. But this comes with a new challenge
of increased complexity. Can cell signaling scientists balance the bewildering complexity
that comes with the discovery power of proteomics technology? Read more...