Immune Checkpoint Blockade in Cancer Therapy: New Insights and Opportunities, and prospects for Cures

James P. Allison

Chairman, Department of Immunology

Director, Immunology Platform

MD Anderson Cancer Center

Houston, Texas USA

The existence of multiple non-redundant inhibitory pathways that limit T cell responses offers novel strategies for mobilizing the immune system to attack cancer cells. The best characterized of these immune checkpoints is CTLA-4, which inhibits T cell proliferation by interfering with the interaction of the costimulatory molecule CD28 with its ligands B7-1 and B7-2 on the surface of antigen presenting cells. Antibodies to CTLA-4 have proven effective against multiple tumor types in both pre-clinical and clinical studies. Ipilimumab, an antibody to human CTLA-4, showed long term (>4 years) survival benefit in about 20% of patients in a randomized, placebo-controlled trial in late stage melanoma. In 2011 it was approved by the FDA for treatment of late stage melanoma and is now a standard of care for that disease.

The mechanism(s) of action of anti-CTLA-4 are still being elucidated. We and others have shown that CLTA-4 limits T cell proliferation by a cell intrinsic mechanism. However, there is also evidence that anti-CTLA-4 has to engage the target on both effector (Teff) and regulatory (Treg) T cells. Thus anti-CTLA-4 exerts its anti-tumor effects by multiple mechanisms.

PD-1, another checkpoint, recruits a phosphatase and seems to interfere with T cell antigen receptor mediated signaling. It has two ligands, PD-L1 and PD-L2, which are both expressed on dendritic cells. However, many tumor cells also express PD-L1. Antibodies to PD-1 and PD-L1 have both shown objective responses against several tumor types in clinical trials with response rates of about 25% . A recent phase II trial of a combination of anti-PD-1 and anti-CTLA-4 in melanoma showed objective responses in about 50% of late stage melanoma patients.

Emerging data suggest that T cell responses are largely directed toward neoantigens arising as a result of mutational events associated with the carcinogenesis. While all tumors with antigens recognizable by the immune system should be targets for checkpoint blockade, it is becoming clear that certain types of tumors with lower burdens of mutations (eg. prostate, breast, and kidney cancer) present special challenges for immune therapy. Strategies for effective treatment of such tumors will be discussed.