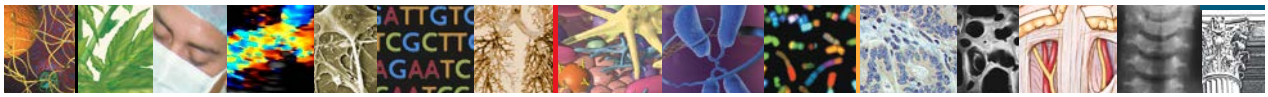

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Perspective

Releasing the Brakes on Cancer Immunotherapy

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After mapping out the molecular mechanisms of T-cell antigen recognition, regulation, and function in the 1980s and 1990s, immunologist James P. Allison hypothesized that blocking negative immune regulators (checkpoints) would give the human immune system the power to fight cancer. His testing of this hypothesis in preclinical models led to the clinical development of a new generation of active agents for cancer treatment. In some subgroups of patients, unleashing native immune-system cells to fight cancer now provides a realistic chance of long-term remission. For this seminal work, Allison, a professor at the M.D. Anderson Cancer Center in Houston, has won the 2015 Lasker–DeBakey Clinical Medical Research Award, announced on September 8.

It had been known for more than a century that occasionally when there was evidence that a patient's immune system had attacked a metastatic cancer, a long-lasting remission occurred. But for a long time, although scientists were aware of the immune system's role, they had no mechanistic understanding of why the immune system worked in a particular patient and why the immune responses could not reliably be repeated. Recognizing the great success of vaccines in preventing infectious diseases, cancer researchers tested multiple vaccines made up of inactivated cancer cells and tried injecting infectious agents into tumors, with the hope of activating the immune system against the cancer. But evidence of clinical responses to these approaches was mostly anecdotal.

Knowledge of immune-system regulation improved over time and led to the testing of recombinant cytokines, such as interferons and interleukin-2, for activating the immune system against cancer. With these agents, tumor responses became more reproducible and sometimes durable, but they were infrequent (achieved in 5 to 10% of patients) and occurred in very few types of cancers, such as melanoma and renal-cell carcinoma.

Nevertheless, these initial clinical experiences showed that immunotherapy had potential in cancer treatment. Further progress would hinge on an understanding of how immune-system cells recognize cancer cells and are regulated to kill them. In his early scientific career, Allison made important contributions to

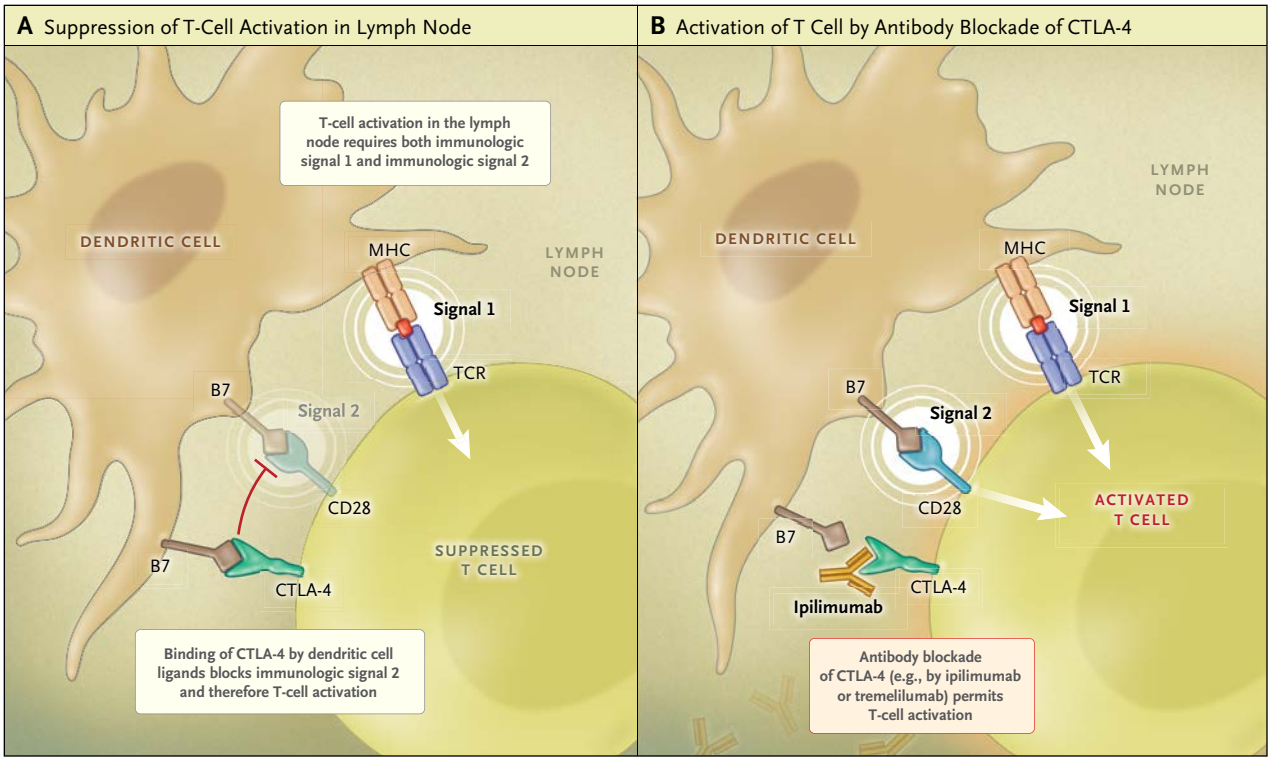

Figure 1. T-cell Activation in the Lymph Node.

Two immunologic signals are required for T-cell activation in the lymph node: stimulation of the T-cell receptor (TCR) by the MHC (immunologic signal 1), and stimulation of CD28 by the B7 costimulatory molecules (immunologic signal 2). However, binding of the B7 costimulatory molecules to CTLA-4 blocks immunologic signal 2, and therefore blocks T-cell activation. Antibody blockade of CTLA-4, for example, by ipilimumab, derepresses signaling by CD28, permitting T-cell activation.

elucidating the rules of T-cell activation, including defining the structure of the T-cell receptor (TCR) that specifically recognizes antigens[1] and demonstrating that the T-cell molecule CD28 provides costimulatory signals necessary for full T-cell activation.[2] The TCR and the CD28 molecule are the molecular basis of what we know as immunologic signal 1 (TCR recognition of antigens) and immunologic signal 2 (costimulation), respectively. Both are required to license T cells to specifically kill their target cells (Fig. 1A).

But solving the puzzle of how an immune response can lead to the eradication of cancer also required understanding how the immune system is specifically activated by certain antigens mostly foreign to the body, rather than by endogenous antigens. Allison then described the inhibitory function of the checkpoint molecule cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), which blocks immunologic signal 2 and thereby prevents T cells from becoming fully activated. In a series of studies in preclinical models, he demonstrated that blocking CTLA-4 with therapeutic antibodies could unleash an immune response against cancer (Fig. 1B).[3] With these studies, Allison shifted the paradigm from attempting to activate the immune system (i.e., vaccinating) to releasing the checkpoints that keep it in a negative regulatory mode.

Checkpoint-blockade immunotherapy has arguably been the most exciting advance made in cancer treatment in recent years. High on the list of scientific achievements in the fight against cancer, it has joined the ranks of radical surgery, radiation therapy, chemotherapy, endocrine therapy, and targeted oncogene therapies. Blockade of CTLA-4 with the monoclonal antibody ipilimumab was the first treatment to improve overall survival in patients with metastatic melanoma and has gained worldwide approval for the treatment of that cancer. Further insights into the release of immune inhibitory checkpoints led to the strategy of "releasing" the programmed cell death 1

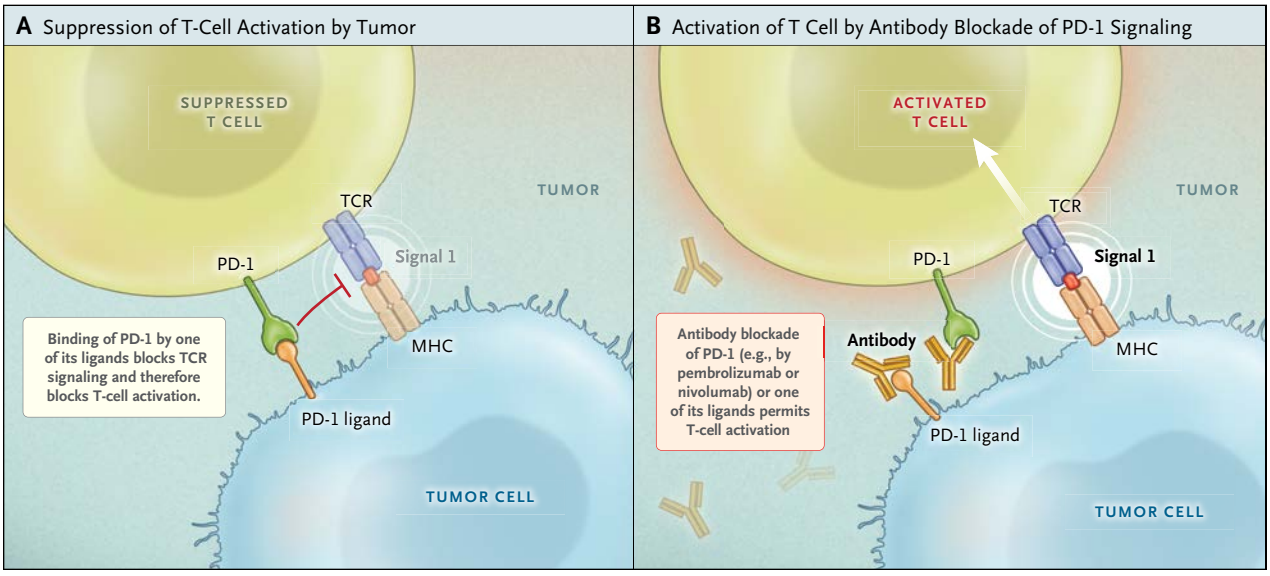

Figure 2. T-cell Activation in Tumor Milieu.

During long-term antigen exposure, such as occurs in the tumor milieu, the programmed death 1 (PD-1) inhibitor receptor is expressed by T cells (Panel A); it suppresses the effect of the TCR on T-cell activation. Blockade of PD-1 or its ligand (Panel B) (e.g., by pembrolizumab or nivolumab) derepresses TCR signaling, thereby permitting T-cell activation.

(PD-1) receptor on T lymphocytes, from which cancer cells protect themselves by expressing the PD-1 ligand 1 (PD-L1) (Fig. 2).[4] Antibodies blocking PD-1 or PD-L1 are in clinical development for the treatment of more than 30 types of cancer, and pembrolizumab and nivolumab, two antibodies blocking PD-1, have gained approval for the treatment of metastatic melanoma and lung carcinoma. Combining CTLA-4 and PD-1 blockade provides even higher response rates than either approach alone in patients with advanced melanoma,[5] highlighting the potential of combination immunotherapy based on blocking immune checkpoints to push the limits of what the immune system can achieve.

In the history of cancer treatment, there will be a full chapter dedicated to unleashing the immune system by releasing its negative regulatory checkpoints. That chapter will start with the seminal studies by Allison involving blocking CTLA-4 in mouse models. As the successful clinical development of ipilimumab and PD-1 and PD-L1 blocking antibodies has shown, Allison's early insight was correct: "What we needed to do was to release the brakes of the immune system to fight cancer." The obvious risk as we push the limits of this approach to cancer treatment is the appearance of autoimmune side effects, which can be serious. But by learning how to safely utilize combinations of immune activators and checkpoint inhibitors, we should be able to expand the potential of immunotherapy for cancer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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