IMMUNOLOGY

The immunotherapy prize!

Lélia Delamarre
Associate Editor.
Email: delamarre.lelia@gene.com

The idea of stimulating the immune system to recognize and destroy cancer is more than 100 years old, but the development of effective immunotherapies has been challenging. The breakthrough came from the work of James Allison and colleagues, who elucidated that regulatory mechanisms fine tune the immune responses to ensure maximal efficacy against infected or abnormal cells without harming healthy tissues. Allison's group and others showed that CD28 and CTLA-A4 are key molecules with opposite roles in the regulation of CD8 T cells, the primary population of immune cells responsible for recognizing and killing cancer cells and infected cells: CD28 enhances T cell activation, whereas CTLA-4 acts as an inhibitory receptor, also called an immune checkpoint, abrogating T cell activation. James Allison went on to postulate that immune responses against cancer cells with high resemblance to normal cells may be suppressed by CTLA-4. He tested his hypothesis in preclinical tumor models and showed that inhibiting this pathway with a blocking antibody against CTLA-4 induces tumor regression by unleashing the antitumor immune response. These results led to the development of ipilimumab, a monoclonal antibody against human CTLA-4, for the treatment of cancer. It was the first immunotherapy to demonstrate survival benefit for patients with metastatic melanoma and was approved by the U.S. Food and Drug Administration in 2011. The remarkable success of ipilimumab laid the foundation for the development of other immunotherapies and, specifically, of drugs that target other immune checkpoints. Since then, antibodies blocking the immune checkpoint PD-1 or its ligand PD-L1 have been developed and commercialized. Remarkable features of these immunotherapeutic agents include their relatively good tolerability and the durability of the responses, which results from induction of long-term memory immunity that can control tumors in patients for years. However, the current immunotherapies targeting immune checkpoints have limitations. Only a relatively small fraction of cancer patients benefit from the current treatment. Additional immune checkpoints that may also be involved in suppressing tumor immunity have been identified, some of which are now being evaluated in clinical trials. The challenge is that multiple pathways likely suppress tumor immunity, and combination therapy will be required to improve responses in a broader number of patients. For example, the blockade of both CTLA-4 and PD-1 pathways is more effective than the blockade of either pathway alone. To improve immunotherapy treatments, in-depth immune monitoring of cancer patients is critical to provide further insights into the basic mechanisms that regulate tumor immunity and to shed light on the impact of immune intervention on tumor immunity. This information will help select patients who are more likely to respond to treatment, allow the design of rational combination therapies that provide optimal benefit to patients, and also help identify new targets for immunotherapy.

James Allison's work has provided insights into key mechanisms that regulate immune responses and was the foundation for the development of the transformative new class of immunotherapy agents, and for this, he received the 2018 Fundación Banco Bilbao Vizcaya Argentaria (BBVA) Frontiers of Knowledge Award in Biomedicine.

– Lélia Delamarre

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