PD-L1 and Immunotherapy

The discovery of a cell protein reveals a new way of harnessing the power of the immune system to fight cancer. Immune checkpoint inhibitors are now showing promise against a wide variety of cancers.

Background

The notion that the human immune system can be enlisted to fight cancer has a long history in medical science, dating back to the beginning of the 20th century. For much of that period, researchers sought ways of strengthening the natural immune response to cancer through the development of therapeutic cancer vaccines and other immune-stimulatory techniques.

As this work was under way, a smaller group of scientists focused on the means by which cancer cells protect themselves from an immune system attack. This latter approach gained momentum in the 1990s, with discoveries about the function of T cell co-receptors in regulating the immune response to disease. It had previously been thought that co-receptors played a purely stimulatory role, inciting T cells to mobilize an immune system assault on infected or malignant cells. Researchers later discovered that some co-receptors act as a brake on the immune response, protecting the body from autoimmune disease. This discovery suggested that blocking such inhibitory co-receptors with drug agents could unleash an immune system attack on tumor cells.

The discovery of PD-L1

In 2000, Dana-Farber Cancer Institute’s Gordon Freeman, PhD, and his colleagues published a study announcing the discovery of the protein PD-L1 (programmed cell death 1 ligand 1) on normal cells. The researchers found that PD-L1 exerts an inhibitory effect on T cells by binding to the T cell co-receptor PD-1, thereby signaling the T cell not to instigate an immune system attack.

A year later, Freeman and his colleagues published a follow-up study, reporting that PD-L1 appears not only on some normal cells but on certain cancer cells as well. The implication was that an agent that blocks PD-L1 (or a related ligand, PD-L2) could release the brakes on an immune system attack on the cancer.

The discovery prompted pharmaceutical companies to pursue the development of drug agents that block PD-1, PD-L1, or PD-L2. Several of these drugs – known as immune checkpoint inhibitors – have recently received Food and Drug Administration (FDA) approval for treating certain types of cancer and are being tested in a variety of other cancers.
Early results of clinical testing

Dana-Farber investigators are now studying which tumor types respond to immune checkpoint inhibitors, the mechanism by which such inhibitors work, and how they can be improved. In early-stage clinical trials, immune checkpoint inhibitors are producing striking results in some cancers. In a phase 1 trial led by Dana-Farber investigators Margaret Shipp, MD, and Philippe Armand, MD, PhD, investigators tested the PD-1 blocker nivolumab in 23 patients with Hodgkin lymphoma who had exhausted numerous other treatment options, often including a stem-cell transplant. Some 87 percent of the participants had experienced a full or partial remission of the disease. The majority of them were still doing well a year and a half after treatment, when the results were published in the *New England Journal of Medicine*. The findings prompted the FDA to designate nivolumab a “breakthrough therapy” for relapsed Hodgkin lymphoma and a multinational phase 2 trial is now under way.

In glioblastoma, researchers led by Dana-Farber’s David Reardon, MD, and Gordon Freeman tested a PD-1-targeting antibody in mice with the cancer. More than half the mice that received the agent were long-term survivors, showing no evidence of tumor in their brain after 50 days. 25-30 percent of those that received antibodies against PD-L1 and CTLA-4 were considered cured. On the strength of these results, Dana-Farber investigators have opened three clinical trials of these agents.

In a phase 1 trial of a PD-L1 inhibitor in patients with bladder cancer, Dana-Farber’s Joaquim Bellmunt, MD, PhD, and his colleagues reported that, after 12 weeks of treatment, there was tumor shrinkage in 52 percent of the patients whose T cells have high levels of PD-L1 prior to treatment. Although more than half of the participants experienced adverse side effects to the drug, known as MPDL3280A, none of them were particularly severe.

Investigators at the Dana-Farber/Brigham and Women’s Cancer Center led by Toni Choueiri, MD, opened their first clinical trial of a PD-1 and PD-L1 blocker for patients with kidney cancer five years ago. Although the results haven’t been published yet, about 20 percent of the trial participants, many with tumors that defied previous treatments, responded to the checkpoint inhibitor. Choueiri and Sabina Signoretti, MD, are analyzing tumor tissue for biological signs that indicate which patients are likely to respond best to the treatment.

Dana-Farber researcher Peter Hammerman, MD, PhD, and his associates are studying the genetics of lung cancer to determine if certain mutations render tumors more susceptible to immune checkpoint inhibitors. David Barbie, MD, is studying whether variations in the immune system from one person to another affect individuals’ cancer-fighting ability. The researchers also are exploring whether as-yet undiscovered checkpoint proteins play a role in turning off an immune system attack and could be targeted in future studies.

One of the hallmarks of immune checkpoint inhibitors has been the durability of the cancer remissions they produce. Unlike some chemotherapy and targeted agents that lose potency as cancer cells develop new genetic mutations.
On the strength of the results in early clinical trials, investigators plan to test immune checkpoint inhibitors against additional types of cancers. While these therapies are likely to be more effective against some malignancies than others, immune checkpoint blockade is rapidly becoming a fixture of the medical arsenal for cancer.

**Selected References**


