Cancer Immunotherapy: The Way to Nobel Prize in Medicine

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The Nobel prize; important and prestigious

On 2018, the Nobel prize in physiology and medicine has been awarded jointly to two immunologists. They were working on the immune checkpoint inhibitors which their research surprisingly led to a state-of-the-art discovery.

The Nobel prize is the most prestigious international award in the world, which annually goes to a number of laureates in the fields of literature, physics, chemistry, physiology or medicine, economics, and peace (1). The physiology and medicine prize (about US$1-million) is bestowed by the Nobel Assembly at the Karolinska Institute (2).

What did the winners solve?

This year, James Allison, Ph.D., and Tasuku Honjo, MD, Ph.D. have shared the Nobel prize for defining a way for cancer treatment by bridging the invention and discovery. Allison and Honjo have been awarded for their long-term research on the cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) and programmed death-1 (PD-1), respectively (3). One of the members of the Nobel committee and also an immunologist named Klas Karre said: "It is all about interference with the brakes of our immune system as a means to unleash this defense and harness it to develop treatment of cancer."

CTLA4 and PD-1 discovered to perform as the brakes of our immune system in which they block the activity of T-cells against tumor cells (4). They function as your car braking system, how would you drive until not releasing the brake pedal?

Allison and Honjo worked independently on the inhibition of negative immune regulation by means of discovering the molecules on the surface of T-cells that prohibit the eradication of malignant cells. Surprisingly, both of the winners, as the basic scientists, were looking for the molecular mechanisms of the immune system and not a method or medication for cancer treatment. But their experiments end into inventing the immune checkpoint inhibitors as the promising medications for treating several types of malignancies and extending lives (3). After announcing Allison as one of the laureates, he stated that 'having his work really impact people was one of the best things he could ever think about'. 'Often I can see my patients telling me', "You saved my life." This is my most enjoyable and, I would say, I'm very pleased to hear what I have done is really meaningful', Hunjo added accordingly.

Allison with the CTLA4

Allison *et al.*, discovered a surface protein on T-cells that acts as a brake of immunity, while working at their laboratory at the University of California, Berkeley, in the 1990s. Soon after, the protein named CTLA-4 became a distinct structure in the autoimmune disease research. Despite the fact that the several scientists were utilizing CTLA-4 on the way of improving the autoimmune disease outcomes, Allison had an eye on triggering cancer cells by blocking this brake. Allison and his co-workers kept working on designing an antibody which was capable of binding to CTLA-4 and initiate the T-cell anti-tumor activity. The designated antibody, named ipilimumab, was the first immune check-point blocker approved by the FDA. The very first animal studies showed a remarkable advance in the cancer treatment so that the mice underwent the experiment had been cured (3, 5). Fortunately, in 2010 results of a clinical trial on the patients with advanced melanoma emerged the outstanding outcome of disease regression in several patients (6).

Honjo with the PD-1

Honjo had started his related research on the molecular biology of the immune system in 1992 in Japan. He obtained another T-cell blocker protein called PD-1. PD-1 also functioned as a brake in the immune system leading to inhibition of T-cell from attacking the malignant cells with a different mechanism from CTLA-4. During the investigations, anti-PD-1 demonstrated as a highly potential antibody

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in order to eradicate cancer cells either in mice or humans (3, 7). It was shown to be effective for bringing long-term remissions from life-threating situations such as metastatic lung cancer (8).

The crossroad of two Nobelists' discoveries

Since two Nobelists' discoveries, there have been vast progressions in the field of check-point inhibitors, especially PD-1 blockers which have had the FDA approval as an effective strategy against malignancies such as renal cancer, lung cancer, lymphoma, and melanoma (3, 7). However, the turning point of cancer immunotherapy was the combination of two different strategies in which the patients' outcomes showed outstanding improvements.

The previous clinical investigations revealed that the combination of CTLA-4 and PD-1 could result in better progression-free survival of untreated melanoma patients in comparison to CTLA-4 monotherapy. Accordingly, the adverse events of the combination therapy are more than utilizing each method separately (9).

Limitations on the way of check-point blockers

The adverse side effects of the check-point inhibitors are caused by the over activity of immune system in the absence of modulating brakes, the condition in which the body encounters an up-regulated immune response that leads to a diversity of symptoms, more likely diarrhea and colitis (9). Although, their most specific and important side effects are immune-mediated colitis, pneumonitis, hepatitis, and endocrinopathies (e.g. hypothyroidism and encephalitis) (10). Early recognition and restricting the side effects by the administration of corticosteroids and other immune-suppressive agents are recommended while prescribing the check-point inhibitors (11).

A number of steps have still remained in order to exploit the body's immune response as a weapon against malignancies and empower it for serving immunotherapy.

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