Waking the Immune System at Last

This CCR Focus section examines a spate of new immunomodulatory agents, the latest in a long list of attempts to recruit the immune system to overcome cancer. Beginning with vaccines more than 40 years ago, we saw the development of interferon and interleukin (IL)-2 and then adoptive therapy with tumor-infiltrating lymphocytes, convincing ourselves in the process of the ability of the immune system to drive cancer into remission. Until recently, melanoma was the cancer considered most responsive to immune therapies, with renal cell cancer a distant second given its single digit sustained remission rate with IL-2. But the demonstration that anti-CTLA4 antibodies could block an immune checkpoint and provoke antitumor immune responses raised the possibility that there were other ways to recruit an immune response and the hope that other cancer types could be successfully treated.

And so it is that oncologists now have cell-based therapies, vaccines, cytokines, and an immune checkpoint modulator in their repertoire. More exciting, though, has been the extension of these therapies beyond melanoma and renal cancer. With Sipuleucel-T, we had the approval of an immune therapy in prostate cancer, whereas studies with the checkpoint inhibitors anti-PD-1 and anti-PD-L1 have given some hope that other solid tumors, including colorectal, ovarian, and non–small cell lung cancer, may be vulnerable. We must now work to see if the immune system will be able to control cancer on a scale few had dreamt possible. But as with all cancer therapies, this story brings with it a cautionary tale. First, immune therapies come at a price and may be associated with significant toxicities that require intensive management. That requirement has led most investigators to avoid IL-2, a therapy with a defined cure rate in a solid tumor we still cannot otherwise cure. Second, immune therapies suffer from the same problem that affects other therapies—the need to predict those who will respond. Third, immune therapies lack what we lack in all of cancer therapeutics—ways to measure treatment effect other than tumor shrinkage or survival. While they are gold standards, we do not learn very much about why therapies do or do not work. Immune response, part of normal physiology, should be eminently measurable, but to date, such assays have not been forthcoming as measures of success for vaccines or other therapies. The field, reinvigorated by its recent successes, should take this unmet and important need to heart.

This CCR Focus series reflects the excitement in the field today. Led by Guest Editors Ignacio Melero and Paolo Ascierto, expert authors Sznol and Chen, Vonderheide and Glennie, Wolchok, Gilboa, and colleagues present new and novel immune therapies in the pipeline, discuss mechanisms by which immune therapies destroy cancer cells, and examine the difficult path toward biomarkers for immune responsiveness. Both the anticipation for the future and the many challenges are illuminated here.

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