Better cancer immunotherapy drugs through X-ray crystallography

31 May 2017

Immunotherapy drugs to combat cancer have stimulated tremendous excitement among patients and physicians alike. They debuted in 2011, when the U.S. Food and Drug Administration approved ipilimumab (Yervoy) to treat metastatic melanoma, a usually fatal disease. Since then, other immunotherapies have reached the market, including pembrolizumab (Keytruda), nivolumab (Opdivo), atezolizumab (Tecentriq) and avelumab (Bavencio).

These first-generation immunotherapy drugs are all monoclonal antibodies which enable the immune system's T cells to attack tumors. However, their promise for treating cancer has also brought peril: the drugs can overstimulate the immune system to attack healthy tissues, causing serious side effects, including death, in significant numbers of patients.

A new paper published online May 8 in *PNAS* by Steven Almo, Ph.D., and his Einstein colleagues, in collaboration with Dr. Alan Korman's team at Bristol-Myers Squibb, reveals for the first time the atomic interactions that occur when ipilimumab binds to its target—important findings that could lead to the design of improved versions of ipilimumab. Dr. Almo is professor and chair of biochemistry, the Wollowick Family Foundation Chair in Multiple Sclerosis and Immunology, and director of the Macromolecular Therapeutics Developmental Facility at Einstein.

T-cell activity depends on several different types of protein receptors present on the T-cell surface. In describing how these receptors govern T-cell activity, Dr. Almo uses an automobile analogy. "Certain proteins on the T-cell surface act as the ignition, since their recognition of infectious microbes or malignant cells turns on the T cell," he says. "But as with a car, you also need an accelerator—a different set of proteins that stimulates the T cell to actually kill the malignant cell it has recognized. Then, at some point, you want to turn off the immune response so T cells don't attack healthy tissues. So additional T-cell surface proteins act as brakes, working in opposition to the accelerator receptors to bring the whole system back to normal again."

Unfortunately, tumors can evade the body's immune response by exploiting T cells' finely calibrated control system. They cunningly express cell-surface proteins that stimulate the very T-cell receptors that put the brakes on T-cell attack, allowing the tumors to remain unscathed.

Current immunotherapy drugs work in the same basic way, preventing tumor proteins from engaging T-cell braking receptors. Two such target receptors have been identified: PD-1 (programmed cell death protein-1) and CTLA-4 (cytotoxic T-lymphocyte antigen-4).

Ipilimumab—the immunotherapy drug that Dr. Almo's PNAS paper focuses on—binds to the CTLA-4 receptors on T cells. This prevents the tumor B7-1 and B7-2 ligand molecules (the "brakes" in this system) from binding to those CTLA-4 receptors and shutting down T-cell activity. (Ligands are molecules that bind to and activate receptors.) But precisely why ipilimumab works at the atomic level was not known.

Dr. Almo and his co-authors used high-resolution X-ray crystallography to construct a detailed three-dimensional model of the key molecular complex formed when ipilimumab binds to its CTLA-4 target. The X-ray crystal structure of the ipilimumab:CTLA-4 complex reveals the atomic interactions underlying ipilimumab's affinity for CTLA-4. In particular, the model shows why ipilimumab is an effective drug: the spatial arrangement of its atoms directly competes with the B7 ligands for binding to CTLA-4.

These insights into the ipilimumab:CTLA-4 complex "provide the foundation for rational design" of more effective and less toxic versions of ipilimumab, the

researchers concluded.

More information: Udupi A. Ramagopal et al. Structural basis for cancer immunotherapy by the first-in-class checkpoint inhibitor ipilimumab, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1617941114