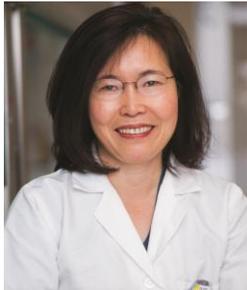


Discovery opens door to new strategy for cancer immunotherapy

New research by Dana-Farber scientists raises the prospect of cancer therapy that turns a tumor's best friends in the immune system into its gravest enemies.

As reported in the journal *Science*, investigators uncovered a mechanism that allows key immune system cells to keep a steady rein on their more belligerent brother cells. These restraint-minded cells normally prevent the immune system from attacking normal, healthy tissue, but in cancer patients they can also dampen an attack on a tumor.

The new study points to a fresh approach to immune system-based therapies for cancer. The attack-suppressing cells retain their suppressive nature only as long as a certain protein pathway within them remains intact, researchers found. If that pathway is disrupted, as by a targeted drug, the cells not only lose their identity, they join in the attack on a tumor.



“By identifying a mechanism responsible for the stability of these suppressive cells, we may be able to block that mechanism in such a way that cells are converted into cancer-fighters,” says Harvey Cantor, MD, who led the study with Hye-Jung Kim, PhD, of his lab, Nick Haining, BM, BCh, of Pediatric Oncology, and an international team of collaborators.

The study grew out of a desire to understand the biology behind a critical aspect of the immune response. In reaction to infection or inflammation, immune system cells known as effector T cells (Teffs) undergo rapid changes – arming themselves and forming groups that target specific diseased cells. A second type of immune system cell, called regulatory T cells (Tregs), remain stable even as Teffs go into battle mode. Such persistence is critical, as the role of Tregs is to keep Teffs under control and prevent them from damaging normal tissue.

Kim set out to discover how Tregs maintain their stoic stability. She noted that Tregs generally had high levels of a protein called Helios, a transcription factor that helps switch genes on and off. She then discovered that Tregs with low levels of Helios were rather unstable – too unsteady to keep the immune response in check.

When she examined mice genetically incapable of producing Helios, she found the animals beset by a T-cell and antibody attack on normal tissue. Moreover, the animals' Tregs had become Teffs and joined the immune system assault.

The results suggest the same effect could be achieved in cancer patients. “Current approaches seek to eliminate Tregs, and thereby increase anti-tumor immunity,” says Kim. “Our findings raise the prospect of achieving a double-barreled effect: by targeting Helios, we may not only reduce the number of Tregs but also convert surviving Tregs into Teffs.”

The researchers are now exploring that possibility. In experiments in mice injected with metastatic melanoma cells, animals that couldn’t produce Helios developed far fewer cancerous nodules in their lungs than normal mice, and survived far longer, researchers found.

“The next step is to identify antibodies and small-molecule drugs that can successfully target Helios or genes in the Helios pathway,” says Kim, whose research focuses on the immune system’s ability to “tolerate” – not attack – normal tissue. Philanthropic support provided by the Schecter Foundation “will allow us to test a variety of such agents that we hope will eventually make their way into the clinic,” Kim says.