MedicalXpress

'Antigen-presenting cell' activates T cells by alerting them to the presence of tumors

July 15 2016, by Liz Droge-Young

Using advanced imaging technology that allowed them to spy on interactions among cells in the lymph nodes of living mice, a research team led by UCSF scientists has identified a cell that is a key player in mounting the immune system's defense against cancer. The finding opens a new avenue for targeted treatments in the rapidly advancing field of cancer immunotherapy.

A class of immune cells known as antigen-presenting cells (APCs) helps to activate the body's defenses against a range of threats, from viruses and bacteria to cancer. As their name implies, these cells work by carrying microscopic pieces of pathogens or tumors to lymph nodes, where the fragments are "presented" to other immune cells known as T cells. In this way, APCs prime T cells to specifically attack the invaders.

"There has always been a missing link between the tumor and the specific immune cells recruited in the lymph node," said UCSF's Matthew "Max" Krummel, PhD, professor of pathology, who led the study. "We wondered, 'What is the cell that bridges those two arenas to continually activate the immune response?'"

As reported in the July 14, 2016 online edition of *Cancer Cell*, a group led by Krummel identified that cell, a specific type of APC known as a CD103 dendritic cell. Additionally, the researchers determined that the CD103 cell must express a protein called CCR7 to properly transport cancer antigens between the tumor and lymph nodes.

Humans have their own version of CD103 dendritic cells, which are known as CD141 cells.

Krummel said that the new work was made possible by advances in a technique known as intravital two-photon microscopy, which enabled the researchers to directly observe interactions between APCs and T cells in lymph nodes of live mice with melanoma tumors.

"Imaging with a two-photon microscope brings veracity," Krummel said. "If you see something happening in the lymph node you don't wonder if it was an artifact of mixing two things in a tissue culture dish. If you see it in vivo, you know it's a real biological phenomenon."

After fluorescently labeling melanoma cells in the mouse model, Krummel and colleagues confirmed that CD103 cells transfer tumor antigens from their origin to the lymph nodes. When the group genetically eliminated CCR7 from CD103 cells, this transport was greatly reduced, and tumors in mice lacking CCR7 grew significantly faster.

Previous research in the Krummel lab had shown that CD103 dendritic cells keep T cells activated within the tumor microenvironment, but the current study illuminated their expanded role. "It turns out that the same cell type we previously studied within tumors also raises the immune alarm within lymph nodes, providing the rest of the body with information about the tumor," Krummel said. "And when it comes to CD103 trafficking, CCR7 is like the address on an envelope."

To investigate the potential consequences of varying CCR7 levels in humans, the researchers mined data from clinical samples including those from The Cancer Genome Atlas, a National Institutes of Health (NIH) database containing genomic and clinical information from thousands of cancer patients. In one example, of 44 applicable patients,

those with higher than average CCR7 expression had more T cells infiltrate their tumors, showing more efficient immune priming. More importantly, whereas those in the lower 50 percent of CCR7 expression died within three and a half years, 65 percent of the top half remained alive over this period.

Current immunotherapy approaches known as checkpoint blockade are focused on ramping up the response of already activated T cells, but the new study opens the possibility of developing "upstream" treatments that aim to get T cells activated in the first place, said Edward Roberts, PhD, a postdoctoral fellow in the Krummel lab and first author of the new Cancer Cell paper. "Understanding which cells are critical for initiating an anti-tumor immune response allows us to start thinking about novel approaches to immune therapy, which could complement the successes achieved in recent years with checkpoint blockade immunotherapy."

To advance this goal, Krummel co-founded Precision Immune, a startup company aimed at boosting the immune response to cancer. The company expects to have pharmaceuticals, based on this and previous Krummel-led work on CD103, ready for clinical trials in the next five years.

"In the war on cancer, we have to try all avenues," Krummel said.

More information: Critical Role for CD103+/CD141+ Dendritic Cells Bearing CCR7 for Tumor Antigen Trafficking and Priming of T Cell Immunity in Melanoma. DOI: dx.doi.org/10.1016/j.ccell.2016.06.003

Provided by University of California, San Francisco

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