Molecule identified that helps give resident T cells in the skin their anti-cancer punch

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Mouse showing signs of vitiligo. Photograph courtesy of Medical University of South Carolina cancer immunologist Dr. Chrystal M. Paulos and Dartmouth's Dr. Mary Jo Turk. Credit: Photograph courtesy of Medical University of South Carolina immunologist Dr. Chrystal M. Paulos and Dartmouth's Dr. Mary Jo Turk.

The molecule CD103 is key to the long-term residence of T cells in the skin and to their anti-tumor function, report a team of researchers at the Medical University of South Carolina (MUSC) and the Dartmouth-Hitchcock Norris Cotton Cancer Center In the April 14, 2017 *Science Immunology*. This finding supplements the ground-breaking discovery by the Dartmouth team, reported in the same article, that T cells residing in the skin are responsible for a potent anti-tumor response against melanoma.

The Dartmouth team, led by Mary Jo Turk, Ph.D., established the crucial role of resident memory T cells in the skin in eliciting a strong protective response against melanoma. The team began by questioning why patients with melanoma who develop the autoimmune disease called vitiligo have such a good prognosis. Vitiligo is an autoimmune skin condition against normal healthy melanocytes. Historically, the development of vitiligo in melanoma patients has been rare, but the recent use of immunotherapies, especially checkpoint inhibitors, has increased its incidence.

MUSC cancer immunologist Chrystal Paulos, Ph.D., and other investigators have previously shown that the most potent forms of adoptive T cell therapy for melanoma cause robust vitiligo in mice. In adoptive immunotherapy, T cells are harvested, amplified or otherwise modified, and reinfused to boost the anticancer immune response. Paulos is an endowed chair in the Department of Dermatology and Dermatologic Surgery, an associate professor in the Department of Immunology and a member of the MUSC Hollings Cancer Center.

Using mouse models of melanoma and vitiligo, the Dartmouth team, in collaboration with Paulos and her laboratory, found that resident memory T cells permanently reside in vitiligo-affected skin, where they kill melanoma cells. Although resident memory T cells were previously known to prevent skin viral infection, it was not known that they could fight tumors.

The collaborative team also showed that resident memory T cells depend on the molecule CD103 for their anti-tumor function in skin. This underscores the unique importance of CD103 for antitumor T cell memory.

"Chrystal [Paulos] has been a long-time friend and collaborator," says Turk. "When we realized that her laboratory was generating potent anti-tumor T cells that expressed CD103, we saw this as a unique opportunity to combine efforts."

Chrystal M. Paulos, Ph.D., is a cancer immunologist at the Medical University of South Carolina (MUSC) and a co-author on the April 14, 2017 *Science Immunology* article. At MUSC, she is an endowed chair in the Department of Dermatology and Dermatologic Surgery, an associate professor in the Department of Immunology and a member of the Hollings Cancer Center.

Credit: Photograph by Sarah Pack, Medical University of South Carolina.

The finding that immune cells in the skin, especially skin showing an autoimmune response, mediate the strongest anti-tumor response is surprising because T cells are traditionally thought to reside in immune organs, such as lymph nodes, spleen, and blood. It has been thought that T cells enter tumors from the blood.

"A lot of people look at the blood to see if there is a response or not. What we should be doing is taking a biopsy of the skin of melanoma patients and asking questions there," says Paulos. "I think we would get deeper information."

These findings open up the possibility of new treatment avenues for patients with cancer.

"Perhaps we can we take advantage of cancer immunotherapy by engineering CD103 and other molecules into T cells so that they home to the skin and remain there," says Paulos. "Perhaps we can also combine resident memory T cells with other therapies such as checkpoint modulators (PD1 blockade) that would ensure a more hospitable environment for the reinfused cells."

The potential applications of resident memory T cells for adoptive immunotherapy are not limited to melanoma.

"We now know that T cells parked where they reside in the skin are the ones eliciting the most potent anti-tumor response," explains Paulos. "But residency isn't just in the skin. If the finding that resident memory T cells are the most potent mediators of immunity holds up in different types of cancer, which I think it will, you could take a biopsy of the lung

or the pancreas, for example, to see if there are resident T cells there. If so, perhaps you could make more resident memory cells for that particular organ to bolster the immune response."

The Dartmouth and MUSC teams plan to write a joint grant so that they can continue to explore these questions together.

More information: Brian T. Malik et al, Resident memory T cells in the skin mediate durable immunity to melanoma, *Science Immunology* (2017). DOI: 10.1126/sciimmunol.aam6346

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