New lipid signaling target may improve T cell immunotherapy

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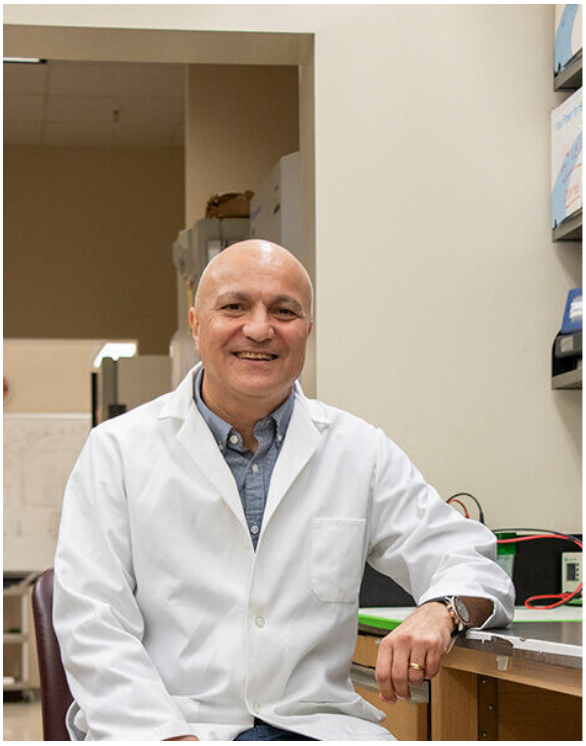

Hollings Cancer Center researchers Dr. Ogretmen (left) and Dr. Mehrotra aim to regulate the fate of T cells. Credit: Emma Vought (left) and Sarah Pack (right)

The immune system surveils our body looking for things that don't belong, often bacteria and viruses. While cancer cells are abnormal cells that undergo unregulated cell growth, they are good at evading detection by the immune system. T cell immunotherapy uses the body's own T

cells but reprograms them to target cancer cells. Three different signaling pathways are known to be important for regulating T cell function: the cytokine interleukin-15 (IL-15) promotes a central memory-like T cell (Tcm) phenotype that can kill unwanted cells, transforming growth factor beta (TGF-β) pushes T cells to differentiate into T regulatory cells (Tregs), and peroxisome proliferator-activated receptor gamma (PPARγ) regulates lipid metabolism, which is important for providing energy to T cells. The mechanism by which these pathways determine T cell function, however, remains unknown.

In recent work published by two collaborative research groups at the Medical University of South Carolina (MUSC) who study lipid signaling in the context of cancer biology and cancer immunology, these three seemingly disparate pathways have been linked. The two groups collaborated to examine the role of sphingosine 1-phosphate (S1P), a lipid generated by sphingosine kinase 1 (SphK1), in regulating T cell differentiation. Their results, published online on August 13, 2019 by *Cell Reports*, showed that loss of SphK1 from T cells and the resulting decrease in S1P levels foster the maintenance of a Tcm phenotype and inhibits their differentiation into Tregs. Ultimately, this signaling pathway improves T cell-mediated immunotherapy.

"A lot of information is known about SphK1 in tumors, but there is little known about how SphK1 regulates T cell function," says Shikhar Mehrotra, Ph.D., co-senior author, Hollings Cancer Center (HCC) researcher, associate director of the Cell Therapy Unit, and associate professor at MUSC.

To evaluate the impact of SphK1 on T cells, SphK1 function was inhibited both genetically and by using a chemical drug. They found that inhibition of SphK1, and therefore reduced S1P levels, led to a Tcm phenotype that reduced tumor size and decreased mortality in preclinical cancer models.

"When we inhibit S1P, generated by SphK1, we can make these T cells more active for killing tumors," says Besim Ogretmen, Ph.D., co-senior author, HCC researcher, program coleader of HCC's Developmental Cancer Therapeutics Research Program, professor and SmartState endowed chair of biochemistry and molecular biology at MUSC. "I think this was the first discovery that internal lipid signaling can play an important role in regulating the function of T cells against cancer cells."

They next worked out the mechanism of how SphK1 influences the T cell phenotype. Depletion of S1P levels increased the activity of a transcription factor that turns on genes associated with the memory phenotype. Additionally, loss of S1P reduced the activity of PPARγ, with two consequences: reduced PPARγ activity prevented T cells from differentiating into Tregs, and reduced PPARγ activity led to an increase in lipid utilization for energy production. Cumulatively, the multiple impacts of S1P depletion led to the Tcm phenotype.

"This is an upstream molecule that regulates T cells in many different ways," says Mehrotra.

These molecular details explain the different impacts of T cell regulation that were known previously. IL-15 leads to a Tcm phenotype by inhibiting SphK1 and S1P; conversely, TGF-β pushes cells towards the Treg phenotype by activating SphK1. Furthermore, these different pathways influence each other to intricately control T cell fate.

"Everything has to be in balance, and it remains that way until an infection increases the signaling when the immune response needs to be hyperactive," says Mehrotra. "Then Tregs need to tolerize our immune system and prevent autoimmunity. However, to combat cancer cells, we need to break that tolerance because we need the T cells to be hyperactive."

Common cancer treatments often center around chemotherapy, which not only targets and kills cancer cells but also kills immune cells. Targeting SphK1 allows the immune cells to stick around to target and kill cancer cells. Furthermore, Mehrotra and Ogretmen have shown that combination therapy, using a drug called PD1 mixed with compounds that inhibit SphK1, increased the efficacy of treatment in preclinical models.

"There is a lot of communication between the cancer cells in the body and the immune cells," says Ogretmen. "We don't really understand this communication yet and whether the cancer cells signal to the T cells to increase their S1P levels, making them more inactive."

Interestingly, S1P levels are high in cancer cells, allowing them to survive better. This might also impact the ability of T cells to target the cancer cells. This new work suggests that depletion of S1P might function in two ways, both inhibiting cancer cell survival and promoting T cell activity.

"This has opened up many interesting areas of further research," says Mehrotra. "Now we know that just by modulating intrinsic levels of S1P you can reach a different phenotype."

"The key is understanding the mechanism of how this pathway regulates T cell function and differentiation," adds Ogretmen.

This work paves the way to calibrate T cell immunotherapy for cancer by dampening the accumulation of S1P. Future work will be aimed at validating this pathway in several preclinical cancer models. While the mechanism of action should not change across the various model systems, this is an important next step in bringing this therapy to the clinic. Furthermore, Mehrotra and Ogretmen think this pathway has the potential to modulate autoimmune diseases such as multiple sclerosis,

lupus and colitis.

More information: Paramita Chakraborty et al, Pro-Survival Lipid Sphingosine-1-Phosphate Metabolically Programs T Cells to Limit Anti-tumor Activity, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.07.044

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