# Th1/17 hybrid T cells offer potent and durable anti-tumor response in preclinical model

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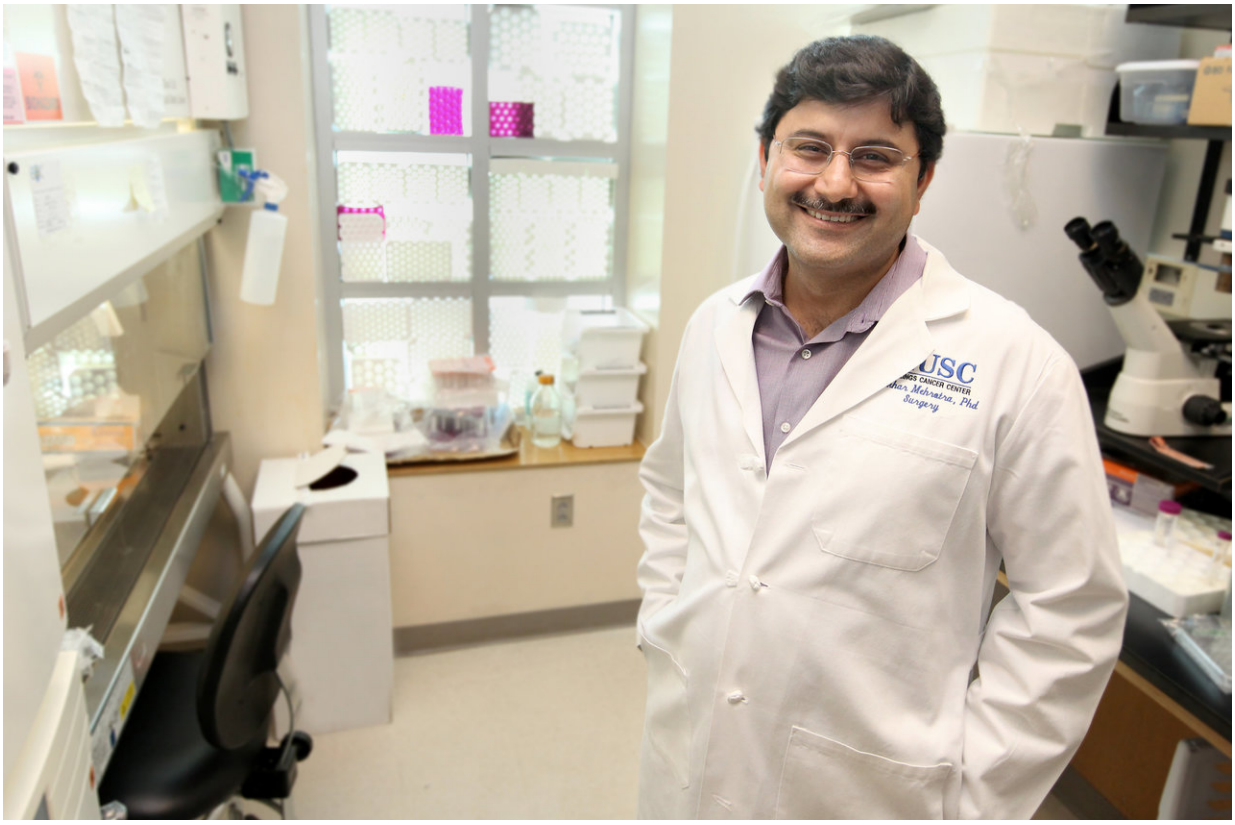


Dr. Shikthar Mehrotra, co-scientific director of the Center for Cellular Therapy at the Medical University of South Carolina and senior author on the Cell Metabolism article on Th1/Th17 hybrid cells for adoptive cell therapy Credit: Sarah Pack. Medical University of South Carolina.

Adoptive cell therapy for cancer involves harvesting T cells from a patient and expanding and sometimes modifying them in the laboratory before reinfusion. It has been challenging to create T cells that are both potent and durable. In a *Cell Metabolism* article, Medical University of South Carolina investigators report the potent anti-tumor properties of hybrid Th1/Th17 cells that combine the cancer-fighting properties of Th1 cells and the ability of Th17 cells to self-renew and regenerate.

In recent years, the search for new cancer treatments has increasingly focused on immunotherapies that harness the body's own defenses to fight tumors. Adoptive cell therapy (ACT) is a powerful immunotherapeutic strategy that can effectively control some cancers but that also has drawbacks. To administer ACT, T cells are withdrawn from a patient and cultivated in a laboratory (ex vivo) for weeks or months, until a massive number of cells are available to be injected back into the patient. During ex vivo cultivation, the T cells often lose potency and life span.

A great deal of research has been aimed at improving ACT effectiveness by enhancing anti-tumor T-cell strength and persistence. While researchers have made incremental progress by changing components of the laboratory culture, it has been difficult to create a T cell that incorporates both desirable anti-tumor attributes (i.e., long-term survival and high cancer-fighting efficacy)—until now.

Shikhar Mehrotra, PhD, associate professor of surgery and co-scientific director of the Center for Cellular Therapy at the Medical University of South Carolina (MUSC), led a team of investigators to develop a culture protocol that successfully merged the strong effector traits of Th1 cells with the durability of Th17 cells, which have a highly stem-like phenotype. The result was a hybrid Th1/17 T cell that has the best anti-cancer characteristics of both parent cells.

"We've known about how T cells can fight tumors for more than three decades. However, for a long time the focus was on Th1 cells because they seemed to be most important. They secrete interferon-gamma, which can directly kill the tumor and also draw in other cells to help fight the cancer," explains Mehrotra. "But in the past ten years we've realized that it's more important to have a T cell with long-lasting function. Th17 cells survive longer than Th1 cells because they have a more stem-like phenotype. So, we wanted to integrate both the robust interferon gamma phenotype of Th1 cells with the long-lasting phenotype of Th17 cells. But it took us some time to figure out how to put them together in a manner that they can also keep their useful traits when injected into the patient. We had to use different cytokines in the laboratory culture and combine them in new ways-it took us a while to get the right recipe."

Because Th1/17 cells are a new cell type, the team extensively investigated their properties using transcriptomic and metabolic profiling and a series of confirmatory experiments. Comparative Illumina microarray analysis showed that 589 genes were exclusively expressed in hybrid Th1/17 cells, which have unique metabolic and T-cell signaling pathway gene expression. Furthermore, comparative studies in a mouse melanoma model demonstrated that adoptive transfer of hybrid Th1/17 cells provided more effective tumor control than Th1 or Th17 cells (reported earlier by this group). Importantly, when tumor-free mice were later re-challenged with the same tumor, there was no tumor growth through 150 days (the last observed time point).

After demonstrating that these novel hybrid Th1/17 cells could persist long-term in the body (in vivo) while maintaining their effectiveness, the researchers next set out to determine what specific cellular mechanisms supported these characteristics. A comprehensive evaluation of principal metabolites showed that the metabolite signature of hybrid Th1/17 cells was intermediate between the original Th1 and Th17 cells. Intriguingly,

Th1/17 cell levels of the metabolite nicotinamide adenine dinucleotide (NAD+) were 34 times higher than in Th17 cells. Furthermore, they discovered that these high NAD+ levels were sustained via glutaminolysis instead of glycolysis-making Th1/17 cells metabolically unique. This is important because metabolic commitment plays an important role in the function and survival of T cells in the tumor microenvironment.

Further experiments found that their enhanced anti-tumor properties were attributable to increased NAD+ mediated histone deacetylase Sirt1 activity. The team showed that pharmacologic or genetic inhibition of either NAD+ or Sirt1 impaired the anti-tumor activity and confirmed that elevated NAD+ levels are required to maintain the anti-tumor activity and in vivo viability of Th1/17 cells.

While these were all important findings, they simply laid the groundwork for what was to be the most important result of their work. Experiments revealed that inhibiting CD38, a NAD+ hydrolase that inversely correlates to NAD+ levels and co-expresses with cell exhaustion marker PD1, led to vastly improved tumor control. In other words, cells with reduced surface expression of NADase CD38 had intrinsically higher NAD+ levels and were much stronger cancer fighters.

The inverse relationship between intrinsic NAD+ levels and TGF-beta-induced CD38 expression may explain how the CD38-NAD+ axis regulates T-cell function in the tumor microenvironment. Results also suggested that, since CD38 and PD1 are tightly co-expressed, CD38 plays a central role in regulating 'metabolic exhaustion' by moderating NAD+ levels in PD1+ exhausted T cells. Most impressively, the team found that blocking CD38 expression resulted in improved tumor control even in unpolarized anti-tumor T-cells. The team treated mice with established melanoma using Th0 cells derived from CD38-KO

(knockout) mice. Results showed that these Th0 T cells could efficiently control tumor growth without ex vivo programming. Thus, strategies targeting the CD38-NAD+ axis could increase the efficacy of ACT.

"We've known about NAD+ for almost 100 years, so, for me, the best part was when we realized that this intrinsic factor was responsible for the cells' strength," says Mehrotra. "That we could pick out one molecule, CD38, and produce this robust anti-tumor phenotype just by knocking it down was a big surprise. I actually thought that it wouldn't work-that we wouldn't get robust tumor control with the CD38 knockout cells. But it turns out that its ability to regulate the important cofactor NAD+ is so vital, that just by inhibiting it we could make the T cells work better."

The MUSC team also used similar ex vivo cultivation conditions to those that produced the hybrid Th1/17 cells to program CD8+ T-cells into a Tc1/17 hybrid phenotype, which also showed potent and durable anti-tumor properties. This finding may have immediate translational value since, unlike Th17 cells, Tc1 cells are known to have better anti-tumor activity despite Tc17 cells' ability to persist longer in vivo. "Using the hybrid programming protocol, we can now use both Th and Tc cells together for ACT," explains Mehrotra.

Overall, the team's experiments suggest that increasing NAD+ may be the key to improving the functionality of any T cell subset, and ex vivo programming to a hybrid phenotype with high NAD+ equates to the intrinsic NAD+ levels achieved by CD38 down-regulation. Better tumor response due to CD38 inhibition that concomitantly increases intracellular NAD+ in T cells (or other immune cells) could contribute to broader use of ACT.

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