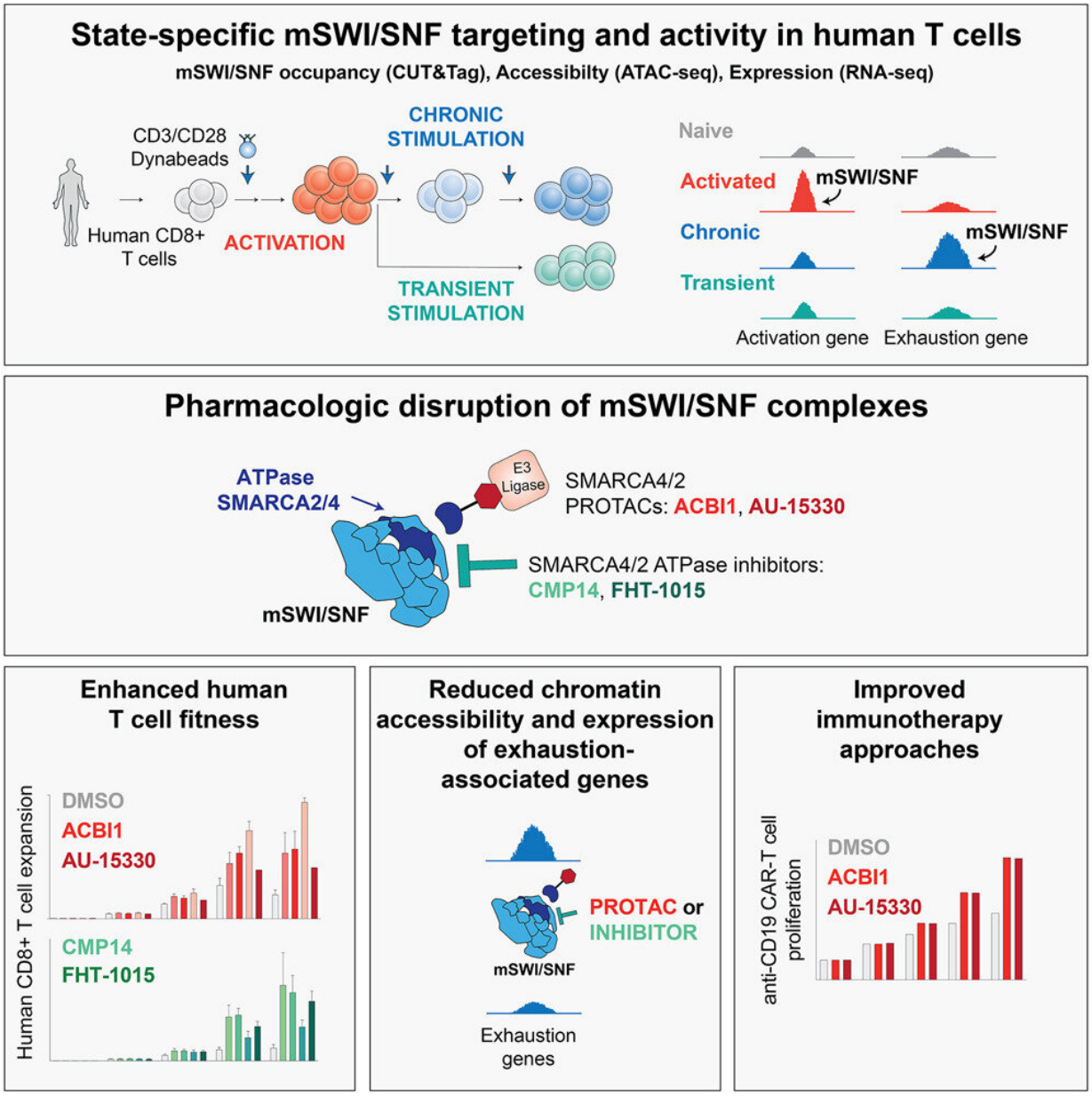
Researchers identify key source of T cell 'exhaustion'

March 20 2023



Graphical Abstract. Credit: *Molecular Cell* (2023). DOI: 10.1016/j.molcel.2023.02.026

Custom-made to attack cancer cells, CAR T-cell therapies have opened a new era in the treatment of human cancers, particularly, in hematologic malignancies. All too often, however, they display a frustrating trait inherited from the body's own immune system cells: a drastic loss of cancer-fighting fervor known as "exhaustion." Exhaustion is not only seen in cancer-fighting T cells but is also frequent in the setting of viral infections, such as human immunodeficiency virus (HIV), hepatitis B/C viruses (HBV, HCV) and COVID-19 (SARS-CoV-2).

The lapse into listlessness has diminished the effectiveness of CAR T-cell therapies in some patients and prompted scientists to try to find its source. In a new study, scientists at Dana-Farber Cancer Institute and NYU Grossman School of Medicine show the commanding role of a specialized group of proteins in the nuclei of our cells, called mSWI/SNF (or BAF) complexes, both in activating T cells to attack cancer and triggering exhaustion.

The discovery, reported online today in the journal *Molecular Cell*, suggests that targeting certain of these complexes, either by gene-cutting technologies such as CRISPR or with targeted drugs, could reduce exhaustion and give CAR T cells (and in general, all tumor-fighting T cells) the staying power to take on cancer.

"CAR T cells and other therapies made from living cells have enormous potential in treating cancer and a range of other diseases," says the study's senior author, Cigall Kadoch, Ph.D., of Dana-Farber and the Broad Institute of MIT and Harvard. "To reach that potential, however, the field had wrestled with the problem of exhaustion. Our findings in

this study indicate new, clinically-actionable ways of addressing this."

CAR (chimeric antigen receptor) T cells are made by collecting thousands of a patient's immune system T cells and equipping them with genes that help them latch onto and destroy cancer cells. After the modified cells reproduce into the millions, they're injected back into the patient, where they strike at cancer cells.

"The problem is that most engineered T cells, like CAR T cells, tucker out," Kadoch says. "They get activated, just as normal T cells in our body do when they encounter an infected or diseased cell, but they quickly stop proliferating and fail to go on the attack. We and other groups have wanted to understand why: what are the determinants of T cell exhaustion?"

Research over the years has suggested that exhaustion (as well as activation and the acquisition of memory-like features) are not controlled by a single gene or a few genes but by the coordination of many genes that together generate an exhaustion "program" for the cell.

Kadoch and her colleagues began focusing on mSWI/SNF complexes years ago as potential regulators of these programs. These complexes, the focus of the Kadoch Laboratory, are large molecular machines that glide along the genome like cursors on a line of text. Where they stop, they can open up DNA strands, switching on genes in that area, and where they disappear from results in the closing of DNA and the shutting off of those genes.

Such complexes qualify as the kind of master switch that could potentially control the exhaustion program. Kadoch and her team decided to track their patterns over the entire course of T cell activation and exhaustion: to determine where they're situated on the genome of battle-ready T cells and how those positions change as exhaustion sets in.

"We did the most comprehensive profiling ever of the occupancy of these complexes in T cells across time, in both mouse and human contexts," Kadoch remarks. "We found that they move around in a state-specific manner, which raises the question of why they move; how do they know where to go in each state?"

The biggest influences on their location, it turned out, were certain transcription factors, proteins critical to activating highly specific sets of genes. The factors guide mSWI/SNF complexes and steer them to precise sites on the genome.

"At each stage of T cell activation and exhaustion, a different constellation of transcription factors appears to guide these complexes to specific locations on the DNA," Kadoch states.

As this profiling work was under way, co-senior author Iannis Aifantis, Ph.D., and his colleagues at NYU Grossman School of Medicine were systematically shutting down genes in T cells to see which ones, when silenced, slowed or stopped the process of exhaustion. "We found that all the top hits in our screen—the genes whose inhibition had the greatest impact on exhaustion—encoded the very mSWI/SNF complexes central to Cigall's lab," Aifantis relates.

"Our labs then together performed a detailed series of joint experiments that showed that if you stifle the genes encoding various components of these complexes, the T cells not only don't get exhausted, but they proliferate even more than before."

The two labs followed up these findings by employing a group of newly-developed small molecule inhibitors and degraders targeting mSWI/SNF complexes. They found that in response to these inhibitors, genes that

promote cell exhaustion became less active while those that spur activation became more active. "We essentially reversed the exhaustion program with these inhibitors," she says, "and resulting cells resembled more memory-like and activated T cell features."

The findings are especially timely given that the first compounds that specifically inhibit the catalytic activity of mSWI/SNF complexes are now being tested in phase 1 clinical trials for cancer. Experiments in animal models of melanoma, acute myelogenous leukemia and other settings hint at the promise of such compounds. In addition to favorable changes in T cells, when the groups treated the animals with CAR T cells that had been exposed to mSWI/SNF inhibitors, tumor growth was reduced.

"Our labs are excited by these findings on numerous fronts- from identifying another important example of the wide repertoire of mSWI/SNF functions in human biology, to the opportunity to target these functions to improve immunotherapeutic approaches for the treatment of cancer and other conditions," says Kadoch. "We have a lot more to do in this space, but this work provides an important new foundations."

More information: Elena Battistello et al, Stepwise activities of mSWI/SNF family chromatin remodeling complexes direct T cell activation and exhaustion, *Molecular Cell* (2023). DOI: 10.1016/j.molcel.2023.02.026

Provided by Dana-Farber Cancer Institute