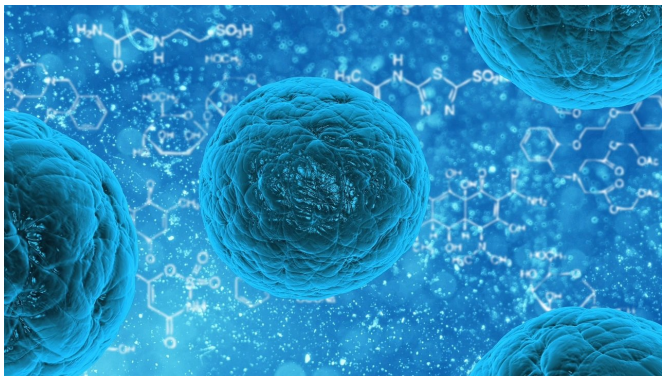
Mitochondria could boost immunotherapy effectiveness

23 April 2021, by Will Doss



Credit: CC0 Public Domain

Boosting mitochondrial function in a subpopulation of T cells could make cancer immunotherapy more effective, according to a recent study published in the *Proceedings of the National Academy of Sciences* (*PNAS*).

Those cells, known as CD1d-restricted natural killer T (NKT) cells, are much more reliant on mitochondrial metabolism during development when compared with conventional CD4+ T cells. That makes those cells an attractive target for boosting immune function in cancer immunotherapy, according to Chyung-Ru Wang, Ph.D., professor of Microbiology-Immunology and senior author of the study, whose findings shed light on possible routes scientists could take to increase their population.

"If we can manipulate these cells, we might be able to make this cell live longer in an immunotherapy context," said Wang, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Conventional T cells are the body's main line of defense against viruses and bacteria. On the other hand, NKT cells are less numerous, but produce far more inflammatory cytokines compared to conventional T cells. This places them in a unique position between the innate or immediate immune response and the adaptive immune response, according to Wang.

"Within hours, the innate immune response begins, but the adaptive response can take more than a week to establish," Wang said. "By producing cytokines and activating other immune cells, these NKT cells can produce a response in about a day."

Wang and her collaborators wanted to examine any differences in T cell development that lead to disparate outcomes among the two groups of T cells.

Studying mice without mitochondria complex III in T cells, the investigators found that while conventional T cells were still present, the population of NKT cells was greatly reduced because NKT cells require stronger signaling from T cell receptors for their development and intact mitochondrial activity for their survival.

This may be a homeostatic mechanism to prevent over-activation of the immune system, according to Wang.

"If these cells never died, they could generate too much immune response," Wang said. "This signaling and metabolic requirement means they die more easily."

However, in a cancer immunotherapy context, keeping these cells alive could be very beneficial. Conventional T cells have thousands of antigen targets, owing to the evolutionary arms race between pathogens and the human immune system.

While this is positive for fighting off infections, this means finding one antigen target that activates

these T cells across many patients with cancer is highly unlikely—the variability from person to person is just too high.

However, NKT cells target lipids, which are largely the same from pathogen to pathogen—meaning a one-size-fits-all approach may be possible. Armed with these findings, Wang said she believes that boosting mitochondrial function may be one way to sustain these cells over the course of immunotherapy, strengthening immune response and the subsequent cancer-killing ability of the treatment.

"Enhancing mitochondrial function in this type of cells could be the key to making them live longer during immunotherapy," Wang said.

More information: Xiufang Weng et al. Mitochondrial metabolism is essential for invariant natural killer T cell development and function, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2021385118

Provided by Northwestern University