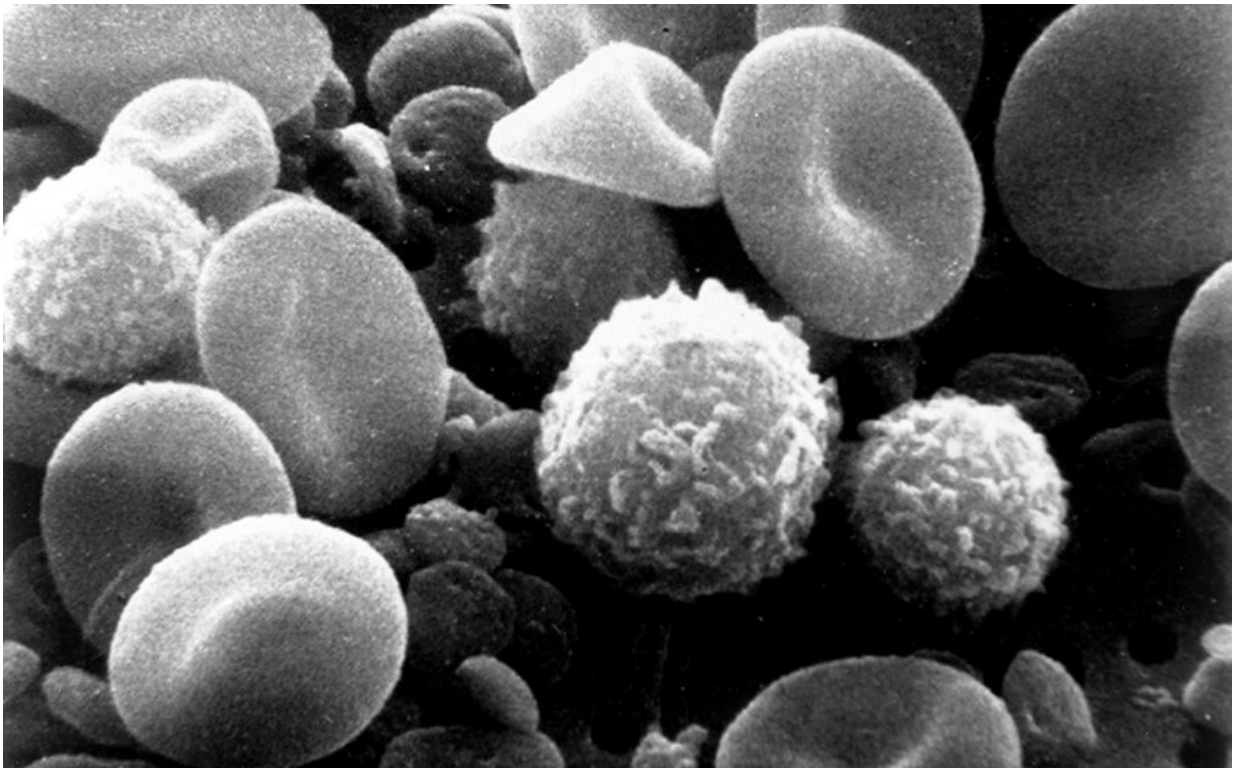
Immune cells have a metabolic backup plan for accessing their anti-cancer playbook

August 22 2024



Myeloid immune cells alongside red blood cells in an electron micrograph of human blood. Credit: National Cancer Institute

Immune cells use two different routes to produce acetyl-CoA, an essential metabolite required to fight infection and cancer, reports a study led by Van Andel Institute scientists.

The findings, published in the *Journal of Experimental Medicine*, could help improve immunotherapies by revealing how diet can boost immune cell function.

"Like any good system, immune cells have a plan A and a plan B," said Russell Jones, Ph.D., the study's corresponding author and chair of VAI's Department of Metabolism and Nutritional Programming.

"We've pinpointed how these cells use a two-pronged approach to ensure they have enough acetyl-CoA to do their jobs and keep us healthy. Importantly, we gained new insights that may inform tailored dietary strategies for augmenting existing cancer treatments."

Cells synthesize acetyl-CoA using nutrients, such as acetate, derived from food. When a threat is detected, cells add acetyl-CoA to certain proteins, which then unlock access to the genetic instructions required to fight disease and infection. Insufficient acetyl-CoA derails the immune system's ability to protect the body.

Until now, however, it was unclear exactly how immune cells maintained their acetyl-CoA reserves. In their new study, Jones and his colleagues identified two routes for acetyl-CoA production—a main route called ACLY and a backup route called ACSS2. Cells prefer ACLY but, in the event of problems, ACSS2 picks up the slack to ensure a continual supply of acetyl-CoA.

Although this type of "metabolic flexibility" has been observed in cancer cells, this is the first time immune cells have been shown to have similar abilities.

The findings also underscore the close relationship between metabolism and epigenetics, which are processes that influence how the instructions in DNA are used without changing the DNA sequence itself. Epigenetic

errors are well-known contributors to cancer and important targets for potential new treatments.

"We identified specific metabolic hubs, which include ACLY and ACSS2, that control cell function through epigenetics," said McLane Watson, Ph.D., the study's co-first author and a postdoctoral fellow in Jones' lab. "This is exciting because these hubs could one day inform new ways to improve cancer immunotherapies by using metabolism to fine-tune epigenetics."

More information: Irem Kaymak et al, ACLY and ACSS2 link nutrient-dependent chromatin accessibility to CD8 T cell effector responses, *Journal of Experimental Medicine* (2024). DOI: 10.1084/jem.20231820

Provided by Van Andel Research Institute