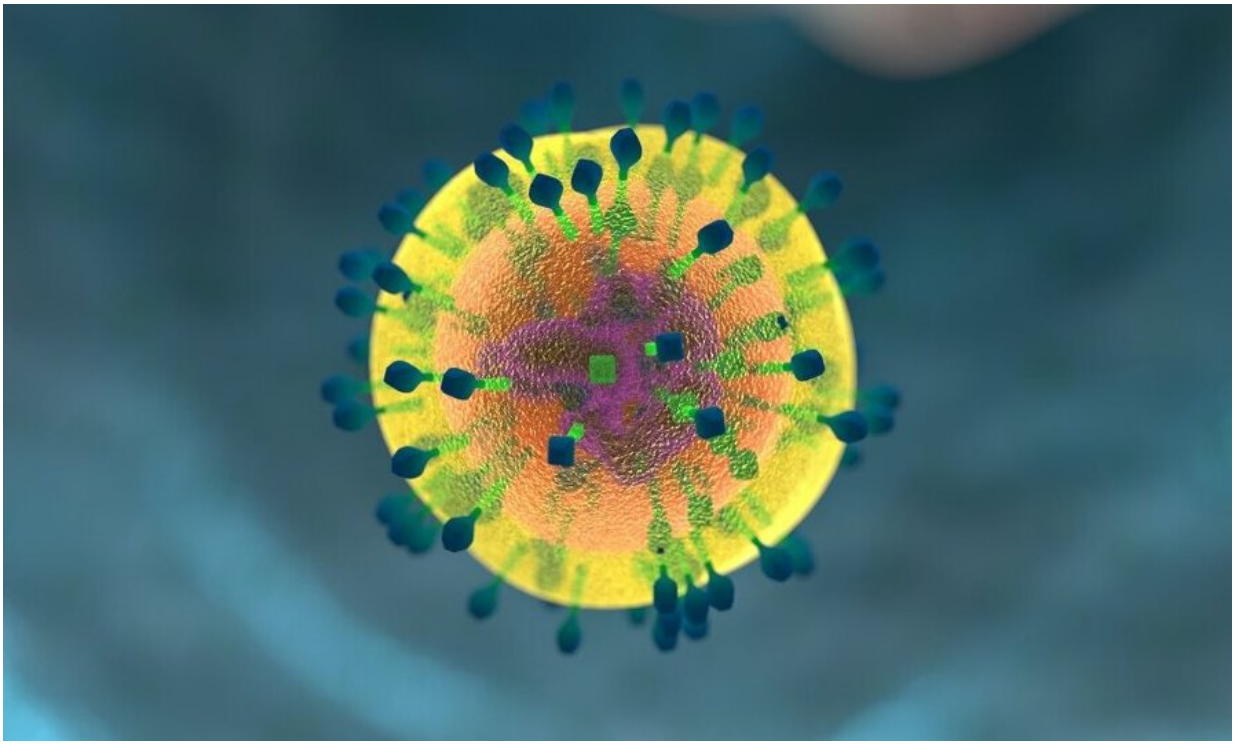
Researchers discover key metabolic process responsible for rapid immune responses

March 15 2024



Credit: Pixabay/CC0 Public Domain

Researchers from Children's Hospital of Philadelphia (CHOP) identified a key metabolite in cells that helps direct immune responses and explains at a single cell level why immune cells that most efficiently recognize pathogens, vaccines, or diseased cells grow and divide faster than other cells.

The findings also indicate that a better understanding of this metabolite and its role in immune response could improve the design of immunotherapies and create longer-lived responses against different types of cancer as well as enhance vaccine strategies. The findings were published online by the journal *Science Immunology* in a paper titled "Single-cell NAD(H) levels predict clonal lymphocyte expansion dynamics."

Antigens are foreign substances that our immune system recognizes and responds to by producing more T and B cells. These cells each have unique receptors that recognize specific antigens and can respond appropriately, and they can "remember" and respond similarly when exposed to the same antigen again.

How well a T or B cell sees its antigen is known as its affinity. This fundamental concept of immunology is how vaccines work. When those T and B cells encounter a pathogen, the body needs the ones that recognize their antigen the best, with high affinity, to divide more quickly to produce more daughter cells and "attack" the invader.

However, the underlying mechanisms as to why high affinity immune cells respond more efficiently have remained a mystery for researchers. After seeing an antigen, the chemistry inside T and B cells needs to change to allow them to properly respond. The researchers in this study wanted to look at metabolism to understand what causes high affinity cells to know that they need to divide more quickly to respond appropriately.

"We wanted to see if specific metabolites were sensitive to T cell receptor affinity and controlled T cell expansion during immune responses," said senior study author Will Bailis, Ph.D., Assistant Professor of Pathology and Laboratory Medicine at CHOP and the Perelman School of Medicine of the University of Pennsylvania.

The researchers identified nicotinamide adenine dinucleotide (NAD) as a key, affinity-dependent component of T cell receptor metabolic reprogramming during the early stages of a T cell activation.

Using flow cytometry, the researchers could look at NAD in single cells immediately after activation and show how it dictates the number of times T cells can divide in the future. Therefore, researchers could essentially predict how T cells behave and how many times they divide based on how much NAD they started with.

Additionally, the researchers found that manipulating how much NAD a cell was allowed to make could control when that cell went from a resting state to wanting to divide, suggesting that the metabolite could be used to improve response in certain T cell-driven therapies or vaccines.

"We believe this work shows how single cell differences in metabolism are a key reason why similar cells sometimes display strikingly different behaviors and that this may provide insight into underlying processes that drive disease and dysfunction that cannot simply be explained by gene regulation or signaling," Bailis said.

"With more work, we also believe that this information could potentially be used to improve vaccine strategies and the response and durability of cell-based therapies used to treat cancer and other diseases."

More information: Will Bailis, Single-cell NAD(H) levels predict clonal lymphocyte expansion dynamics, *Science Immunology* (2024). DOI: 10.1126/sciimmunol.adj7238.
www.science.org/doi/10.1126/sciimmunol.adj7238

Provided by Children's Hospital of Philadelphia