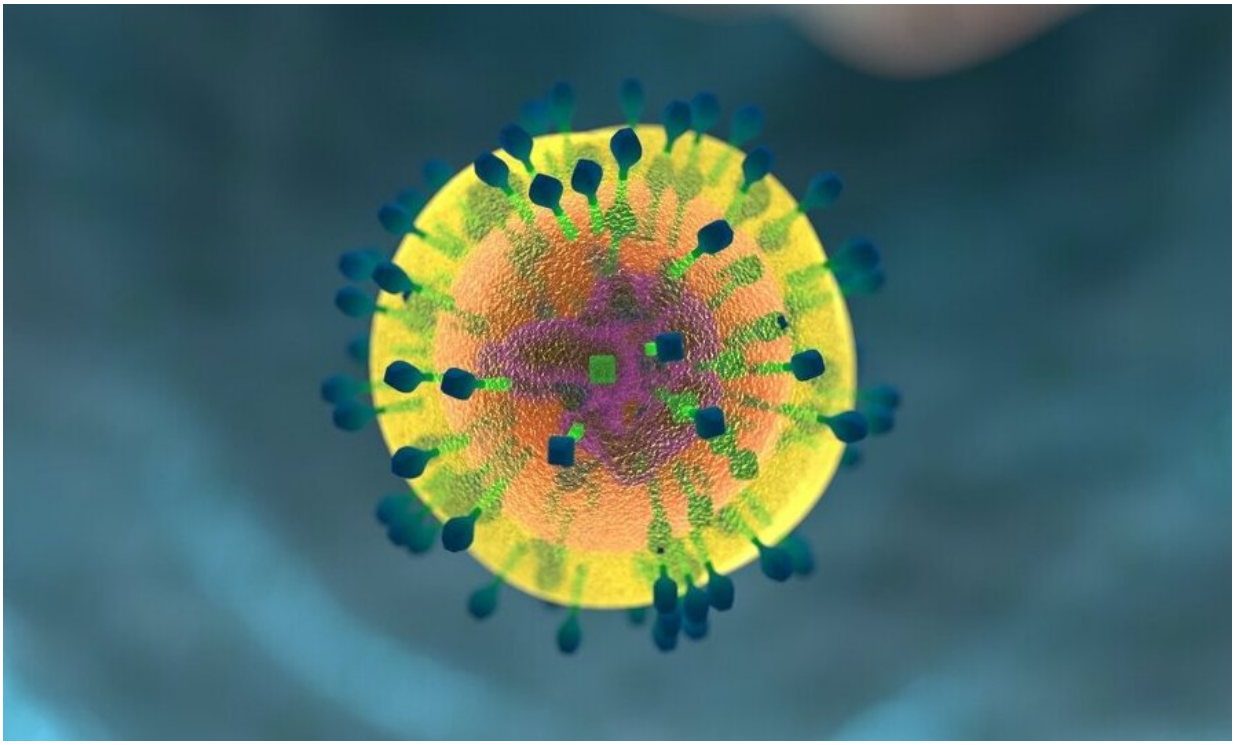
T-cell receptor discovery has huge potential for engineering custom immune responses

October 25 2023



Credit: Pixabay/CC0 Public Domain

T cells are soldiers on the front lines of the human immune system. They are responsible for many important roles, including attacking viral- or bacterial-infected cells and certain cancer cells, and immunological memory—remembering the specific pathogens or the cancer signatures that originally trigger T cells.

Until now, understanding how a T cell forms into a specific role, for example a cell-killing (cytotoxic) T cell or memory T cell, has eluded us. In a paper published in *Cell Reports* on October 25, ISB researchers made the discovery that the genetically encoded T-cell receptor (TCR) sequence that humans develop in early childhood determines a T cell's function.

"That receptor sequence is the major determinant—not signaling proteins such as cytokines or other blood components," said Daniel Chen, first author of the paper. "It is that receptor sequence—the proteins on the T cell that bind to foreign antigens—that determines what this cell's phenotype is, and thus determines what its function is going to be."

In a human clinical study involving 68 patients, the team explored around 700 T cells that specifically interacted with antigens from either SARS-CoV-2, influenza, or cytomegalovirus.

The potential of this fundamental discovery is promising for developing custom immune responses to specific antigens.

"T-cell receptor-engineered T cell cancer immunotherapies are an emerging treatment for solid tumors. In such therapies, the T cells that comprise the drug are typically engineered to aggressively kill cancer cells. We know that a successful immune response requires a balance of T cell phenotypes, some of which kill tumor cells, but others which can form memory or do other functions," said ISB President and Professor Dr. James R. Heath, corresponding author of the paper.

"We show that there is basically a card catalog available," Heath added. "If you want to engineer a balanced immune response, you go to that card catalog, you find the particular TCR genes that, when engineered to build the cell therapy, can provide that balanced response."

A different "card catalog" is required for different antigens. However, many antigens are immunogenic, meaning that for different patients afflicted with the same disease, their T cells will often target the same antigen.

"This is important because it means that what we learn for one patient is likely going to be applicable for another," said Chen.

More information: Daniel Chen et al, T cell receptor sequences are the dominant factor contributing to the phenotype of CD8+ T cells with specificities against immunogenic viral antigens, *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.113279. www.cell.com/cell-reports/full … 2211-1247(23)01291-3

Provided by Institute for Systems Biology