T cell antigen discovery via signaling and antigen-presenting bifunctional receptors.

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Public Summary:
A cell that is infected with a pathogen—for example, HIV—will display a bit of the invader's genetic material on the cell surface, like waving a red flag to indicate what is going on inside the cell. These "flags" are called antigens. Antigens are not limited to the marks of foreign invaders, though—they can be signatures of cancer. When a T cell finds a cell displaying its target antigen, the T cell will bind to it and destroy it. Sometimes this process can lead to autoimmune diseases if T cells begin to target healthy cells. There are one- to five million unique T cells on average in a human, encoding for as many as [approximate number] different pathogens. Though scientists can characterize the shape and molecular makeup of a T cell's receptor, it is difficult to determine what target a given receptor specifically recognizes. In fact, less than 1,000 antigen-T cell pairs are known. This method involves adding a so-called signaling domain to an antigen on an antigen presenting cell. The resulting molecule, also called a SABR, causes the cell to glow green once it has been bound by a corresponding T cell. In this way, a scientist could take thousands of different antigens, each attached with a SABR presenting a unique antigen, and present them with a particular T cell. Only the cells presenting the correct antigen should glow green, allowing one to fish out the correct antigen, which will be the T cell's target.

Scientific Abstract:
CD8(+) T cells recognize and eliminate tumors in an antigen-specific manner. Despite progress in characterizing the antitumor T cell repertoire and function, the identification of target antigens remains a challenge. Here we describe the use of chimeric receptors called signaling and antigen-presenting bifunctional receptors (SABRs) in a cell-based platform for T cell receptor (TCR) antigen discovery. SABRs present an extracellular complex comprising a peptide and major histocompatibility complex (MHC), and induce intracellular signaling via a TCR-like signal after binding with a cognate TCR. We devised a strategy for antigen discovery using SABR libraries to screen thousands of antigenic epitopes. We validated this platform by identifying the targets recognized by public TCRs of known specificities. Moreover, we extended this approach for personalized neoantigen discovery.

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