Study Maps Process Used by T Cells to Discriminate Pathogens

Medical Design Technology

Researchers have for the first time mapped the complex choreography used by the immune system's T cells to recognize pathogens while avoiding attacks on the body's own cells.

The researchers found that T cell receptors -- molecules located on the surface of the T cell -- first bind with the antigen on the pathogen-invaded cell. That initiates a signaling process which leads a co-receptor on the T cell to also bind with the molecule that presents the antigen, amplifying the effect. The process resembles how a person at a party might recognize someone they don't know well by using that person's strong handshake or distinctive voice to supplement their recollection of facial features.

"We show for the first time the important role of the co-receptor in contributing to the discrimination process that takes place in the T cell," said Cheng Zhu, a Regents professor in the Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "This is a cooperative binding process with the co-receptor co-engaging with the T cell receptor. This cooperative binding has a synergistic effect that amplifies the action."

The resulting binding, which then triggers the body's defensive activities, is stronger than the sum of the individual binding that would result from the T cell receptor and CD8 co-receptor operating independently.

The two-step binding process, which alters the accepted model for T cell recognition, was reported Jan. 20 in the early online edition of the journal *Immunity*. The research was sponsored by the National Institutes of Health and the National Multiple Sclerosis Foundation.

Zhu and his colleagues found a time delay between when the T cell receptor engages the antigen peptide and when the CD8 co-receptor goes into action. That delay was about a second in the hundreds of contacts studied. The researchers also found that the binding feedback loop was rapid, short-lived, reversible, synergistic and peptide-discriminative.

The research used a technique known as micropipette adhesion frequency assay to study the mechanical interactions between T cells and the antigen, known as a peptide major histocompatibility complex (pMHC) -- a glycoprotein.

For the study, pMHC molecules taken from a transgenic mouse were placed onto a red blood cell held by a micropipette, simulating the activity of antigen-presenting cells which normally isolate these foreign molecules and display them for

recognition by T cells. A mouse T cell held by another micropipette was then placed into contact with the red blood cell for varying periods of time.

By microscopically examining adhesion between the two cells when separated, the researchers were able to determine whether binding between the T cell receptor -- and the CD8 co-receptor -- had occurred.

In studying the data from hundreds of contacts between different types of antigens, the researchers saw a step in the probability of binding, then a jump to a second step. By alternately blocking binding between the pMHC and the T cell receptor, and between the pMHC and the CD8, they were able to determine that the first step represented binding with the T cell receptor while the second step represented binding with the CD8.

The micropipette adhesion technique, developed by Zhu and his student, allows the study of interaction between T cell receptor molecules -- of which there are as many as a million -- and pMHC protein molecules. Earlier techniques had isolated the receptor molecules for study in a solution environment, but Zhu believes his two-dimensional technique provides a more realistic representation of their activity because the receptors remain on the T cell membrane.

Until now, scientists had assumed that T cell receptor and CD8 binding with the antigen took place at approximately the same time, reinforcing one another to make the intermolecular connection strong enough to trigger an immune response.

"What was surprising to us was that the two interactions do not occur simultaneously," said Zhu. "There is a delay of about one second, and we attribute that to the intracellular interactions that have to take place within the T cell before the CD8 can engage."

The research confirmed earlier findings that T cell responses to lower affinity antigen ligands were more dependent on CD 8 binding. "We confirmed this finding, but demonstrated that the major function of CD8 was to amplify recognition of the higher affinity antigen, meaning the magnitude and kinetics of the CD8 contribution favors the response to low levels of strong antigens," Zhu explained.

T cell receptors are among the most important molecules in the immune system because of their role in recognizing the antigens on target cells. The receptors also must distinguish those threats from the body's own cells to avoid triggering an unwanted immune response.

For the future, Zhu would like to clarify what advantages the two-step process provides when a tiny amount of "non-self" antigen peptides are presented together with a large amount of "self" peptides, and attempt to understand how the T cells seek out interactions with foreign antigens.

In addition to Zhu, the research team included Ning Jiang, Jun Huang, Baoyu Li, and Yan Zhang of the Coulter Department. Collaborators from Emory University included Lindsay J. Edwards, Carrie D. Beal and Brian D. Evavold. Evavold, an associate

professor in Emory University's Department of Microbiology and Immunology and a collaborator of Zhu's in this project, provided the transgenic mouse T cells and pMHC used in the research.

"This new study adds significantly to the understanding of how T cell receptors and associated molecules differentiate the antigens of the body's own cells from those of an invader," Zhu added. "It may be that this co-receptor plays a role in helping discriminate viruses that have mutated and are no longer a direct match to what the T cell is looking for. That's another hypothesis we hope to study."

Research News & Publications Office
Georgia Institute of Technology
75 Fifth Street, N.W., Suite 314
Atlanta, Georgia 30308 USA

Media Relations Contacts: John Toon (404-894-6986)(jtoon@gatech.edu [1]) or Abby Robinson (404-385-3364)(abby@innovate.gatech.edu [2]).

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