Researchers Go Fishing, Pull Out Antigens

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DENVER — Researchers at National Jewish Medical and Research Center have developed a method for finding the molecular targets of the immune system, known as antigens. The method extends a widely used technique, called library display, to more complex proteins. It could have broad applications in biological and medical research. The research team, led by National Jewish and Howard Hughes Medical Institute immunologist John W. Kappler, PhD, is already collaborating with teams looking for causes of the autoimmune disease rheumatoid arthritis, developing cancer vaccines, and understanding the molecular triggers of chronic beryllium disease. The technique is described in the April 2004 issue of PloS Biology, *a publication of the Public Library of Science.*

"Our technique allows us to fish in a vast library of protein fragments for the specific ones that bind to T cells and trigger an immune-system attack," said Dr. Kappler. "We believe that researchers using this technique will extend its usefulness beyond T-cells and antigens to interactions involving a wide variety of biologically important proteins."

T cells are the sentinels of the immune system. Millions of T cells circulate in the body looking for infectious organisms or other foreign invaders. Each T cell carries a receptor that can recognize a specific protein fragment. Cells known as antigen-presenting cells display on their surfaces these protein fragments bound to a molecule known as MHC. When a specific T cell encounters a protein-MHC complex its receptor can bind, it becomes activated. That sets off a cascade of events that tells the immune system to attack that protein fragment and the organism it comes from.

In most cases it is very difficult for scientists to determine what protein-MHC complex a particular T-cell receptor binds, and thus where the immune system is aiming its attack. Dr. Kappler, who was one of the original discoverers of the T-cell receptor, knew that it could be extremely helpful for both basic biological research and medical applications to know what protein a particular T cell bound to.

He and his colleagues developed a system for doing that. Using genetic constructs and baculoviruses, they created a small ocean of insect cells, each one displaying a single MHC molecule holding a specific protein fragment. They then fished in this ocean with soluble T-cell receptors containing fluorescent tags. When the receptors bound distinct MHC/protein complexes, the researchers isolated the insect cells displaying them. They then sequenced DNA in the baculovirus infecting the insect cells, and identified the protein fragments that the receptor bound. Thus, they could identify the specific protein fragment any given T cell is designed to bind.

They are currently working with other researchers to identify protein target in the autoimmune disease rheumatoid arthritis. Other researchers have identified specific T cells that are more common among patients with rheumatoid arthritis, but have been unable to identify the proteins in the body that they bind. If they can identify that protein, it could have major implications for both prevention and treatment of the disease.

Dr. Kappler and his colleagues are also working with other researchers who are developing cancer vaccines, which use specific proteins to activate the immune system to attack cancer cells. The research team is also working with another group to identify the protein that works in concert with beryllium molecules to sensitize the immune system.

Media Contacts

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