Scientists identify trigger for crucial immune system cell

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Scientists at The Scripps Research Institute (TSRI) have identified the long-sought activating molecules for a rare but crucial subset of immune system cells that help rally other white blood cells to fight infection.

In the process, the team also uncovered a previously unsuspected link between the mammalian immune system and the communication systems of simpler organisms such as bacteria.

The findings, published online ahead of print on October 16 by the journal *Immunity*, could lead to novel therapeutic approaches for diseases such as type 1 diabetes that are the result of immune system overactivity, as well as new ways to boost the effectiveness of vaccines, according to study leader Luc Teyton, a professor in TSRI's Department of Immunology and Microbial Science.

A Bridge

When a virus, bacteria or foreign substance invades the body, specialized cells known as dendritic cells present in the skin and other organs capture the trespassers and convert them into smaller pieces called antigens that they then display on their cell surfaces. White blood cells known as T and B cells recognize the antigens to launch very specific attacks on the invaders.

Dendritic cells also activate a specialized population of T cells known as

natural killer T (NKT) cells. Once activated, NKT cells can commandeer the functions of dendritic cells to make them more effective and also recruit and coordinate the responses of T- and B-type cells.

"Because of their dual functions, NKT cells are a bridge between the body's innate immunity, which is characterized by rapid but less specific responses to pathogens, and adaptive or acquired immunity, which is composed of specialized white blood cells that can remember past invaders," Teyton said.

Previous studies indicated that NKT cells are activated by molecules known as glycolipids that dendritic cells produce and then display on their outer surfaces. It was widely assumed that the activating molecules were a class of glycolipids known as beta-glycosylceramides, an important component of nervous system cells.

However, this hypothesis had not been thoroughly examined, in part because there is no chemical test currently available to distinguish between two forms of the molecule that have slightly different configurations—beta-glycosylceramide and alpha-glycosylceramide. In addition, when scientists attempt to create either form synthetically for testing, there is always the possibility of small contamination of one by the other.

"When you're making glycolipids, there is no completely faithful way of controlling the form that you're making," Teyton said. "You're favoring the making of one, but you cannot say for sure that you don't have a small amount of the other form."

A Surprising Result

In their new study, Teyton and his colleagues, who included scientists from Brigham Young University, the La Jolla Institute for Allergy &

Immunology and the University of Chicago, abandoned the chemical approach altogether. Instead, they combined a series of biochemical and biological assays to create a test that was sensitive enough to distinguish between the two different forms of glycolipids.

"Biological assays are exquisitely sensitive to low amounts of otherwise unmeasurable molecules," said study first author Lisa Kain, a research technician in Teyton's lab.

The scientists used custom antibodies to identify and eliminate alpha-glycosylceramides from their test batches. When the team was confident that their test batch contained only beta forms of the glycolipid, they tested it on NKT cells gathered from mice. To their surprise, however, nothing happened. Contrary to the conventional wisdom, the beta-glycosylceramides failed to activate the NKT cells.

"We were very skeptical about the early results," Teyton said. "We thought we had used the wrong antibody."

Next, the team combined enzymes designed to digest molecular linkages found only on beta-glycosylceramides with mice NKT cells inside test tubes. Surprisingly, the NKT cells were still being activated.

Finally, when the team used antibodies to disable alpha-glycosylceramides inside live mice, not only did the NKT cells fail to activate, they disappeared altogether from organs such as the thymus, where NKT cells are produced.

These multiple lines of evidence strongly indicated that it was the alpha form of the glycolipids that were the triggers for NKT cells. "What we thought was the contaminant turned out to be the activating molecule we were looking for," Teyton said.

New Therapies

The results were surprising for another reason. Until that moment, scientists did not think mammalian cells were capable of producing alpha forms of the glycolipids. The molecules were thought to exist only in bacteria and other simple organisms, which use them primarily as a means of communicating with one another. The findings thus suggest that the roots of a crucial part of the mammalian immune response are even more ancient than previously thought.

"Nobody expected this," Teyton said. "It's like discovering that all languages share a common origin."

Now that scientists know that alpha-glycosylceramides are made by our own body and activate NKT cells, they might be able to exploit it to create new therapies. For example, Teyton said, researchers could use enzymes to reduce alpha-glycosylceramide levels in order to suppress an overactive immune response, which happens with diseases such as type 1 diabetes. Or they could combine the molecules with antigens to create vaccines that elicit a faster and more efficient immune response.

"This opens up an avenue of new therapeutic approaches that we've never even thought about," Teyton said.

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