"SHAPELY" GERMS SHAPE UP THE IMMUNE SYSTEM

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-- Only the Right "Fit" Triggers an Anti-Infection Response

Like shoppers in search of the perfect pair of jeans, the body's special immune system cells apparently have assistants that help them rapidly "try on" different pieces of a microbe to find one piece that's shaped just right to fit their cellular skins, Johns Hopkins scientists report.

Working with flu viruses to see how these sentinel cells work, the Hopkins team discovered that they first feel out a microbe's chemical "shape" until they find a section that fits tightly into grooves on their surfaces.

"It turns out that these immune cells do this very well with a bit of help from a protein assistant that gets rid of ill-fitting microbe parts to speed up the trying-on process," says Scheherazade Sadegh-Nasseri, Ph.D., associate professor of pathology, biophysics and biophysical chemistry. A report on the work appears in the January edition of *Nature Immunology.*

Researchers long have known that the immune system needs the "assistant" protein DM to set up the infectious, recognizable part of a germ-the antigen-so that the anti-infectious attack can begin. Cells missing DM can't do this at all. The new Hopkins work shows that they actually oversee the selection of the best-fitting antigen, too.

In experiments measuring the length of time an antigen stays stuck, DM makes sure an infected cell holds onto a microbe long enough to catch the attention of immune cells in the first place, Sadegh-Nasseri says.

To uncover DM's expanded job, Sadegh-Nasseri isolated a protein antigen from the flu virus as a test case and found that cells with DM normally hold on for about six days, long enough for symptoms like sniffles and fever, as signs of immune battle, to develop. When they removed DM from normal cells, the cells did not bind the flu antigen at all. Later, when they mutated the antigen-binding part of the cell, the flu antigen "fell off" after only 10 minutes.

When the scientists studied the 3-D shape of the part of the cell that tries on the antigen, they discovered that the antigen fell off after 10 minutes whether DM was there or not, but only when one specific chemical bond was disrupted.

"DM somehow alters this chemical bond to make antigens fall off a thousand times faster than usual," says Sadegh-Nasseri. "We couldn't believe our eyes when we saw it." Ill-fitting antigens were kicked off in 10 minutes and replaced. Better fitting antigens, like the flu antigen, held on for days.

"We think that as the cell tries each of the thousands of different antigens found on an invading microbe, DM monitors how well each antigen fits by somehow disrupting this special chemical bond," says Sadegh-Nasseri. "Somehow, the better fitting ones are resistant to DM's assault and stay stuck-these antigens ultimately are presented to immune cells to start the infection-fighting battle."

"Just like trying on those designer jeans, if the jeans feel better with the top button undone, it's probably not the best fit," she added.

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Authors on the paper are Kedar Narayan, Chih-Ling Chou, AeRyon Kim, Isamu Hartman, Sarat Dalai, Stanislav Khoruzhenko and Sadegh-Nasseri, all of Hopkins.

On the Web:
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