Scientists discover how protein trips up germs (w/ Video)

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If bad bacteria lurk in your system, chances are they will bump into the immune system's protective cells whose job is gobbling germs. The catch is that these do-gooders, known as macrophages, ingest and destroy only those infectious invaders that they can securely hook and reel in.

Now, Hopkins scientists have shown that a healthy immune response depends on a protein called TRPV2 (pronounced trip-vee-two) which, they discovered, is the means by which macrophages capitalize on brief and accidental encounters with nasty bugs.

Reporting in Nature Immunology in the January 31 online edition, the team proves that TRPV2 is necessary not only for macrophages to get a good grip on disease-causing bacteria, but also as the first line of defense, rallying the rest of the immune system to dispose of the most slippery and sizable germs.

"Imagine a fisherman who gets a bite, but is not strong enough to reel it in alone, so he sounds an alarm that brings others in to help," analogizes Michael Caterina, M.D., Ph.D., associate professor of biological chemistry, Johns Hopkins University School of Medicine. "That's similar to what's happening here: A macrophage receptor will bind to a giant germ it encounters, but not tightly enough to secure it. So TRPV2 on the macrophage acts as an alarm: It tells the other receptors around the macrophage to consolidate in that one place to enhance the local binding of that bacteria."

Ten years ago, Caterina was the first to clone TRPV2 along with a related protein, called TRPV1, which was found to be involved in sensing painful heat. His lab first looked at the nervous system in an attempt to ferret out TRPV2's function, but changed tack when it became apparent that this protein is abundant in the immune system, particularly in macrophages.

To learn what role TRPV2 might play in fighting infection, Tiffany Link, a graduate student in Cellular and Molecular Medicine, harvested macrophages from the bellies of two sets of mice: a "wild type" control group, and a group that had been genetically engineered to lack TRPV2. She grew the normal immune cells and the engineered mutant cells in separate dishes, and then added latex beads that were coated with antibody molecules. The normal immune cells efficiently gobbled the beads, while the mutant cells lacking TRPV2 couldn't ingest nearly as well, indicating that TRPV2 was important in proper functioning of macrophages.

Because the defective macrophages weren't completely inept in their germ-eating job, Caterina suspects that other proteins like TRPV2 are likely players, too, but TRPV2 clearly makes the germ-clearing process more efficient.

Link, who investigated each separate step macrophages take to successfully consume bacteria, found that in the mutant cells lacking TRPV2, the problem existed from the very moment of initial contact with a germ.

"Without TRPV2, macrophages don't bind bacteria and engulf them right away," Link says, "and as a result, the rest of the immune system doesn't get involved and clear the infection," Link says.

In order to find out if a mouse missing TRPV2 would be more

susceptible to bacterial infection, Link injected live bacteria into the bellies of wild-type mice and those lacking TRPV2. The mice lacking TRPV2 died within four days of infection — significantly sooner than the wild types which died within eight days after infection.

Citing the fact that TRPV2 is important not only in helping macrophages to bind to germs, but also in clearing bacterial infection, Caterina noted its potential as a useful drug target. And in cases of autoimmune diseases — arthritis, lupus and asthma, for example — it's possible that the inhibition of TRPV2 might help pull back an overactive immune system.

"We think there are going to be a lot of implications beyond just prevention of infectious diseases where this research about TRPV2's function in macrophages might be relevant," Link adds. "Macrophages consume cholesterol and contribute to hardening of the arteries. They also clear out debris when nerves are injured so that new nerves can grow through that area."

Provided by Johns Hopkins Medical Institutions

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