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Microbes start immune response by sneaking inside cells

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Immune cells that are the body's front-line defense don't necessarily rest quietly until invading bacteria lock onto receptors on their outside skins and rouse them to action, as previously thought. In a new paper, University of Michigan scientists describe their findings that bacteria can barge inside these guard cells and independently initiate a powerful immune response.

The study, published online ahead of print in the April issue of the journal *Immunity* and accompanied by a special commentary, adds important new details to an emerging picture of how the body recognizes invading bacteria and responds. The work of the U-M team and researchers elsewhere — now taking place in laboratory animal studies — offers a different way of thinking about how best to design future human vaccines, as well as drugs that could more precisely target the body's inflammatory response in rheumatoid arthritis and some other autoimmune diseases.

"In our study, the presence of bacterial microbes inside the cell is what triggers the immune response. That creates a new perspective for developing new drugs," says senior author Gabriel Nunez, M.D., the Paul H. de Kruif professor of pathology at the U-M Medical School and a member of the U-M Comprehensive Cancer Center.

For years, scientists have believed that when bacteria invade the body, they set off alarms in the immune system by interacting with receptors on a cell's surface. But, now new studies are revealing that bacteria can

also plunge inside immune system cells and trigger the immune response there. In the new study, Nunez' team sheds light on one major pathway in which this process occurs.

When invading bacteria enter immune system cells, a protein called cryopyrin, present in the fluid inside the cells, responds and activates a key pathogen-fighting molecule, Nunez' team reported last year in Nature. Cryopyrin is implicated in the development of several inflammatory syndromes characterized by recurrent fever, skin rash and arthritis.

Cryopyrin triggers a key enzyme involved in the body's inflammatory response, capsase-1, which in turn causes production of IL-1beta, a powerful molecule which signals the immune system to attack pathogens and induces fever to help the body fend off infection. IL-1beta plays an important role, too, in excessive immune system activity in inflammatory diseases.

The researchers report in the new paper how cryopyrin is activated to start the process. In experiments that exposed mouse immune cells called macrophages to bacteria, Thirumala-Devi Kanneganti, Ph.D., a U-M research investigator in pathology, and Mohamed Lamkanfi, Ph. D, a U-M research fellow, the study's co-first authors, find that cryopyrin's call to action inside the cells occurs without requiring a well-known set of cell-surface receptors called Toll-like receptors or TLRs.
"We prove that these TLRs are not required to activate cryopyrin. That is a major step," says Nunez.

Instead, bacteria were able to enter the cells through a pore in the cell membrane, and stimulate the cryopyrin-initiated immune response without activating TLRs. The researchers discovered that a protein called pannexin-1 creates the pore, like a devious undersea diver drilling a hole in a ship hull.

The team's work joins a growing body of research revealing the importance of recently discovered receptors such as cryopyrin inside cells, known collectively as NOD-like receptors. Knowledge about NOD-like receptors is moving forward rapidly and will contribute to a fuller understanding of the human immune system, say the U-M researchers.

Source: University of Michigan