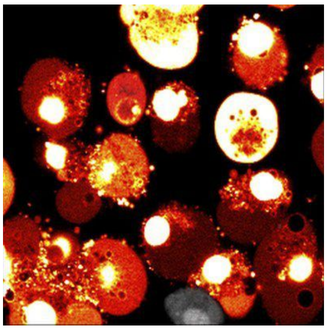
Researchers Identify a New Pathway that Triggers Septic Shock



Cells called macrophages explode when bacteria enter them and trigger an immune response through a sequence of events that UNC researchers uncovered. Credit: Jon Hagar and Ine Jørgensen.

The body's immune system is set up much like a home security system; it has sensors on the outside of cells that act like motion detectors — floodlights — that click on when there's an intruder rustling in the bushes, bacteria that seem suspect. For over a decade researchers have known about one group of external sensors called Toll-like receptors that detect when bacteria are nearby.

Now, researchers at the University of North Carolina School of Medicine have identified a sensor pathway inside cells. These internal sensors are like motion detectors inside a house; they trigger an alarm that signals for help — a response from the immune system. This research, published in the Sept. 13, 2013 issue of the journal *Science*, indicates that both exterior and interior sensors work together to detect the same component of bacterial cell membranes, a molecule called lipopolysaccharide or LPS.

By showing how the immune system distinguishes between suspicious activity and real threats, the study could lead to new therapies for septic shock — when the immune system overreacts to a bacterial infection to such an extent that it causes more harm than good.

"During the defense against an infection you want to be able to differentiate between the bacteria that stay on the outside of the cell and the ones that get inside," said senior study author Edward A. Miao, MD, PhD, assistant professor of microbiology and immunology. "You can think of the exterior sensors as a yellow alert; they tell us that bacteria are present. But these bacteria could either be simple ones in the wrong place, or very dangerous ones that could cause a serious infection. The interior sensors act as a red alert; they warn us that there are bacteria with ill intent that have the genetic capacity to invade and manipulate our cells."

About half of the cases of septic shock are caused by bacteria that produce LPS, also known as endotoxin. In fact, much of what is known about endotoxic shock comes from studying animals injected with high doses of LPS. For example, previous studies pinpointed the role of the Toll-like receptor 4 gene (TLR4) as a sensor on the outside of cells; mice without that gene resisted endotoxic shock.

In a study published in January 2013, also in the journal *Science*, Miao and his colleagues showed that a sensor called caspase-11 sounds an alert when bacteria enter a cell. However, it wasn't clear which of the thousands of molecules that make up a bacterial cell triggers that new sensor.

In the current study, Miao and his colleagues investigated which bits of foreign material were being detected. They took apart and delivered different chunks of bacteria into the cytoplasmic compartment inside the cell. To their surprise, they found that the caspase-11 sensor inside the cell was detecting the same molecule, LPS, as the TLR4 sensor outside the cell. The researchers wondered whether there was a link between these two sensors.

Through a number of experiments in animal models of sepsis, Miao's team showed that the exterior and interior alarms work together through a two-step defense mechanism: LPS is first seen on the outside of the cell by TLR4, which sets the interior caspase-11 alarm into a watchful state. At very high doses, the LPS crosses into the cell, tripping the caspase-11 alarm. The end result is the generation of the red alert signal, which causes the cell to explode, a form of cell death called pyroptosis. During an infection, the immune system essentially burns the house down around the invading bacteria, depriving it of a place to replicate, and exposing it to more potent immune defenses. During sepsis, however, too much fire leads to the onset of shock.

Miao says that figuring out how these two sensors get activated in response to a bacterial infection could help researchers develop new ways of preventing or treating septic shock, a condition that kills about half its victims.

"The septic shock we see in patients is probably a lot more complicated than what we see in this experimental system," said Miao. "The next question we need to ask is whether these same sensors are going off in people with septic shock, and if so, is there a way to block them so we can keep patients from dying."

Study co-authors from UNC were Jon A. Hagar and Youssef Aachoui. The work was done in collaboration with Robert K. Ernst and Daniel A. Powell at the University of Maryland in Baltimore. This work was supported by NIH grants AI007273 (J.A.H), AI097518 (E.A.M), AI057141 (E.A.M), and AI101685 (R.K.E).

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