Team discovers how cells distinguish friend from foe

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(Medical Xpress)—Researchers at UC Davis have shown how the innate immune system distinguishes between dangerous pathogens and friendly microbes. Like burglars entering a house, hostile bacteria give themselves away by breaking into cells. However, sensing proteins instantly detect the invasion, triggering an alarm that mobilizes the innate immune response. This new understanding of immunity could ultimately help researchers find new targets to treat inflammatory disorders. The paper was published in *Nature* on March 31.

The immune system has a number of difficult tasks, including differentiating between cells and microbes. However, the body, particularly the digestive tract, contains trillions of beneficial microbes, which must be distinguished from dangerous pathogens.

"We are colonized by microbes. In fact, there are more bacteria in the body than cells," said senior author Andreas Bäumler, professor and vice chair of research in the UC Davis Department of Medical Microbiogy and Immunology. "The immune system must not overreact to these beneficial microbes. On the other hand it must react viciously when a pathogen invades."

The key to distinguishing between pathogenic and beneficial bacteria are their differing goals. Ordinary digestive bacteria are content to colonize the gut, while their more virulent cousins must break into cells to survive. *Salmonella* achieves this by activating enzymes that rearrange the actin in a cell's cytoskeleton. Fortunately, cellular proteins sense the active enzymes, leading to a rapid immune response.

In the study, the researchers investigated a strain of *Salmonella*, in both cell lines and animal models, to determine how the innate immune system singles out the bacteria for attack. *Salmonella* uses a secretion system, a type of molecular syringe, to inject pathogenic proteins, such as SopE, into the cell. SopE activates human GTPase enzymes RAC1 and CDC42, which break down the surrounding actin, allowing the bacterium inside.

But breaking and entering has consequences. Sensing the active GTPase enzymes, and recognizing their pathogenic nature, a protein called NOD1 sends the alarm, signaling other proteins, such as RIP2, that the cell is in danger. Ultimately, this signaling pathway reaches the protein NF-?B, a transcription factor that instructs the genome to mount an immune response, activating genes associated with inflammation, neutrophils and other immune functions.

Though it had been hypothesized that GTPase activation might trigger an immune response to attacking bacteria, prior to this study, no one had identified the pathway to NF-?B. These results were somewhat surprising, as NOD1had been thoroughly studied; leading many researchers to conclude it had no further mysteries to divulge. No one expected it to play such a significant role in alerting the innate immune system that cells were under attack.

These results could help researchers find new targets to combat inflammatory diseases. For example, NF-?B is known to be involved in a variety of conditions, such as inflammatory bowel disease, arthritis, sepsis and others. By understanding the pathways that activate inflammation, scientists and clinicians can develop ways to inhibit it.

"These pathways might be triggered erroneously because the host thinks there's an infection," said Bäumler. "Knowing the pathways and how they are activated is critical to controlling them."

Provided by UC Davis