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The typhoid fever pathogen uses a cloaking mechanism to evade neutrophil neutralization

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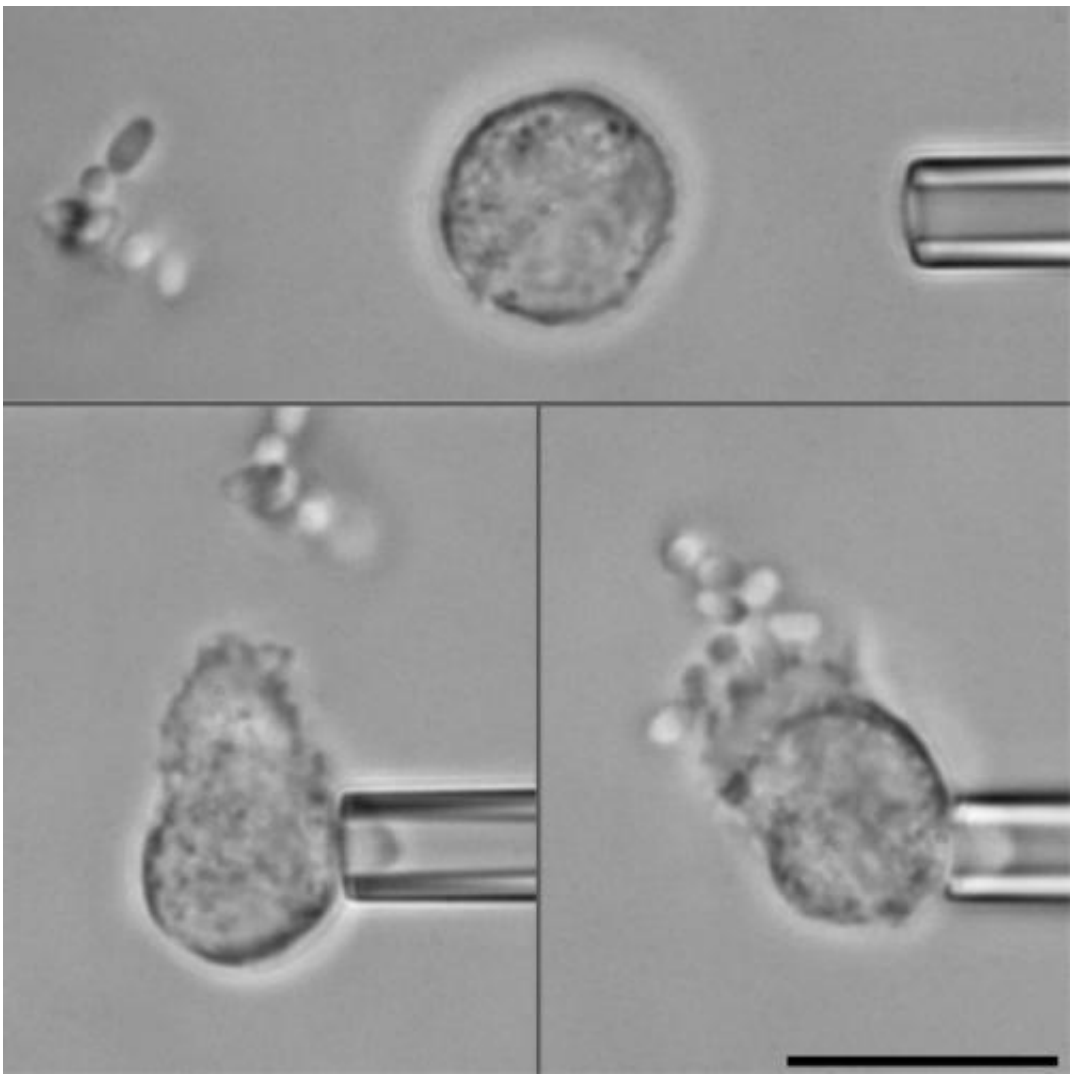

This image depicts a single cell experiment in which a human neutrophil was picked up by a micropipette (top panel) and brought into close contact with *S.*

Typhimurium cells immobilized by optical tweezers. The neutrophil extends a pseudopod towards the bacteria (left bottom panel) and is allowed to phagocytose the pathogen (bottom right panel). Credit: Heinrich & Bäumler, et al. CC-BY

Typhoid fever is caused by systemic (body-wide) infection with *Salmonella enterica Typhi*. In contrast, infection with the closely related bacterium Salmonella enterica Thyphimurium is usually limited to the gut and causes less serious diarrheal disease. Research published on August 7th in *PLOS Pathogens* comparing the two pathogens reveals how *S. Typhi* avoids recognition and elimination by patrolling immune cells called neutrophils, allowing it to disseminate throughout the patient's body.

Neutrophils track down microbial invaders and gobble them up. To investigate why some Salmonella strains trigger a neutrophil response but others don't, researchers led by Volkmar Heinrich and Andreas Bäumler from the University of California at Davis, USA, designed a way to directly observe the interaction between a single bacterium and a single neutrophil cell. They immobilized the bacterium with laser tweezers in close proximity to a neutrophil held by a tiny glass pipette.

A close encounter with *S. Typhimurium* provokes an obvious response by the neutrophil: the initially round immune cell bulges out towards the bacterium, getting ready to make contact and ingest the intruder. Proximity to *S. Typhi*, in contrast, stimulates no visible changes. This differential response depends on a "natural" immune response environment, that is, on the presence of human blood serum.

To get at the signals revealing the presence of *S. Typhimurium*—which are somehow absent in (or obstructed by) the presence of *S. Typhi*—the

researchers used a second experimental set up. In a so-called Boyden chamber, either bacteria or chemicals that attract neutrophils are concentrated in a bottom compartment that is filled with human blood serum. Neutrophils are initially concentrated in the upper compartment, and their migration to the bottom is quantified.

As expected, the presence of *S. Typhimurium* caused migration of neutrophils to the bottom compartment. This response was blocked by a drug that inhibits the complement system, a part of the non-specific immune system present in human blood. As for the difference between *S. Typhimurium* and *S. Typhi*, the researchers could show that a particular part of the outer layer of *S. Typhi*—the so-called Vi capsular polysaccharide—was responsible for inhibiting the complement-dependent attraction of neutrophils. When they generated *S. Typhi* lacking the Vi capsular polysaccharide and tested them in both experimental settings, they found that these behaved just like *S. Typhimurium*, i.e. evoked the "reach-out" response in pipette-held neutrophils and, in the Boyden chamber, elicited migration of neutrophils to the bottom compartment.

Because the researchers found that mouse neutrophils behaved just like human neutrophils in these experiments, they then tested whether they could recapitulate the difference "in vivo", i.e. in mice infected with both intact *S. Typhi* and with *S. Typhi* lacking the Vi capsular polysaccharide. Indeed, in these mice, neutrophils were found preferentially in association with the latter bacteria. Finally, in mice with a defective complement system, there was no visible preference of neutrophils for either of the two types of *S. Typhi*.

The data, including striking videos*, the researchers say, "illustrate that the Vi capsular polysaccharide can act as a "cloaking device" that makes *S. Typhi* practically "invisible" to neutrophils". Their results, they add, "suggest that one of the differences between [milder] gastroenteritis and

[dangerous] typhoid fever is that the pathogen causing the latter disease evades neutrophil chemotaxis".

More information: Wangdi T, Lee C-Y, Spees AM, Yu C, Kingsbury DD, et al. (2014) The Vi Capsular Polysaccharide Enables Salmonella enterica Serovar Typhi to Evade Microbe-Guided Neutrophil Chemotaxis. *PLoS Pathog* 10(8): e1004306. DOI: 10.1371/journal.ppat.1004306

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