Nature study demonstrates that bacterial clotting depends on clustering

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Bacteria can directly cause human blood and plasma to clot—a process that was previously thought to have been lost during the course of vertebrate evolution, according to new research at the University of Chicago, National Institute of Allergy and Infectious Diseases, and Institut Pasteur in Paris. Their findings will be published online Nov. 2 in *Nature Chemical Biology*.

The discovery will improve scientists' understanding of coagulation during bacterial infections and may lead to new clinical methods for treating serious medical conditions such as sepsis and anthrax.

It has long been known that blood often coagulates during sepsis or bacterial infections, but this has generally been regarded as a host's immune and inflammatory response. It also has been known that bacteria can activate factors that precede coagulation, but it had not previously been known that bacteria can pass the coagulation threshold and cause blood clots to form. Once they form, the clots can grow and propagate. Although this may help prevent the dissemination of the bacteria through the host, it often leads to serious vascular damage due to blocked and injured blood vessels.

The key to clot formation is the location of the bacteria, rather than the total number of bacteria or their level of concentration. In other words, for those bacteria that can activate coagulation factors, coagulation occurs only when a cluster of bacteria forms.

"Our research demonstrates that coagulation can be controlled by changing the spatial distribution, or clustering, of bacteria," said study co-author Christian Kastrup, Post-Doctoral Assistant at the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology. "Therefore, considering the location of bacterial cells, instead of just their presence or absence and their total numbers, could significantly change our understanding of coagulation."

Kastrup, who worked on this research as a graduate student in the Ismagilov Lab at the University of Chicago's Department of Chemistry, is the first author of the Nature paper. Rustem Ismagilov, Professor of Chemistry at the University of Chicago, is the corresponding author. Researchers at the National Institute of Allergy and Infectious Diseases, Institut Pasteur in Paris, and Ben-May Department for Cancer Research at the University of Chicago co-authored the paper.

Coagulation can occur if enough proteases that activate coagulation accumulate near the bacteria, rather than diffuse away. This research used Bacillus anthracis, the anthrax-causing pathogen (using a safe strain that does not infect humans). It found that in the case of human blood, coagulation required the secretion of zinc metalloprotease InhA1, which activated prothrombin and factor X directly—not via factor XII or tissue-factor pathways.

"We refer to this mechanism as 'quorum acting' to distinguish it from quorum sensing, in which bacteria coordinate certain actions based, in part, on their density," said Wei-Jen Tang, Professor at the Ben-May Department for Cancer Research.

This work opens up a new field of study, he added. "We will now explore the commonality of quorum acting, and how quorum acting can affect evolutionary dynamics."

The results of this research have broad implications, according to Ismagilov. "The work emphasizes the importance of bacteria's spatial distribution, rather than just its average concentration in the functioning of nonlinear biochemical networks," he said.

Source: University of Chicago