Scientists identify blood component that turns bacteria virulent

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Scientists from the Scripps Research Institute have discovered the key chemical that signals *Bacillus anthracis*, the bacterium that causes anthrax, to become lethal. This finding opens up new avenues of exploration for the development of treatments for bacterial infections.

The study was published in the November 21 edition of the journal *PLoS Pathogens*.

The Scripps Research scientists identified bicarbonate, a chemical found in all body fluids and organs that plays a major role in maintaining pH balance in cells, as providing the signal for *Bacillus anthracis* to unleash virulence factors. Without the presence of the bicarbonate transporter in the bloodstream, the scientists found, the bacteria do not become virulent.

Scientists have known for some time that bicarbonate is implicated in many diseases, but controversy has existed about whether bicarbonate, carbon dioxide, or some combination of these two molecules are responsible for triggering bacterial pathogenesis. This study confirms, for the first time, that it is indeed bicarbonate, rather than carbon dioxide, that signals the gram-positive B. anthracis to become virulent. This finding also is significant because other pathogenic bacteria such as Streptococcus pyogenes, Escherichia coli, Borrelia burgdorferi, and Vibrio cholera have bicarbonate transport pathways similar to B. anthracis and thus are likely to have similar virulence triggering mechanisms.

Gram-positive bacteria are the major culprits driving the increase of community and hospital acquired bacterial infections. The Centers for Disease Control and Prevention estimates that as many as 10 percent of all patients, or about 2 million people, contract hospital acquired infections each year. These bacteria are often resistant to multiple antibiotics, making the problem a growing public health concern and the need for new antibacterial treatment more urgent. Now, the bicarbonate transporter pathway may be investigated as a potential new target for drug intervention.

"How a bacterium recognizes signals in the host that trigger pathogenesis mechanisms, and the nature of the mechanisms necessary to develop pathogenesis, remain poorly understood," said Scripps Research Associate Professor Marta Perego, Ph.D., who conducted the study with Scripps Research postdoctoral fellow Adam Wilson, Ph.D., and colleagues. "We have identified an essential component for the induction of virulence gene expression in response to host bicarbonate levels and have used this finding to learn more about the extracellular and intracellular signals controlling virulence."

Theory Confirmed

Perego's latest discovery builds on her lab's expertise in the study of bacterial virulence signaling and in the regulatory networks responsible for pathogenicity in other gram-positive bacteria. Her interest in bicarbonate transport pathways as bacteria virulence signaling mechanisms grew out of an early observation that growth of B. anthracis in carbon dioxide and sodium bicarbonate strongly induced toxin production in the laboratory setting. The mechanism behind this observation, however, was never uncovered.

"It was observed that the best medium for toxin production was one that people believed mimicked conditions found in the blood of a human or

animal host, where anthrax bacteria would find both carbon dioxide and bicarbonate. But we've never known which of these two molecules was the more important for bacterial pathogenesis, and whether this belief was correct," Perego said. "Now, we know that it is bicarbonate and that the growth in the presence of bicarbonate really mimics the host growth conditions."

In their current study, the Perego lab identified a previously unknown ATP-binding cassette transporter (ABC-transporter)—which is identified by the gene number BAS2714-12—that was shown to be essential to transporting bicarbonate. As a group, ABC-transporters use the energy of ATP hydrolysis to transport various substrates across cellular membranes. In this case, when the genes that code for the BAS2714-12 ABC transporter were deleted, the rate of bicarbonate uptake inside the cell greatly decreased, induction of toxin gene expression did not occur, and virulence in an animal model of infection was abolished. Elimination of carbon dioxide production within the bacterial cell had no effect on toxin production, suggesting that CO2 activity is not essential to virulence factor induction and that bicarbonate, not CO2, is the signal essential for virulence induction.

"In light of these findings, investigation of bicarbonate regulation and transport should be of much greater significance to a large number of pathogenic organisms," Perego said.

Source: Scripps Research Institute