New contrast agents detect bacterial infections with high sensitivity and specificity

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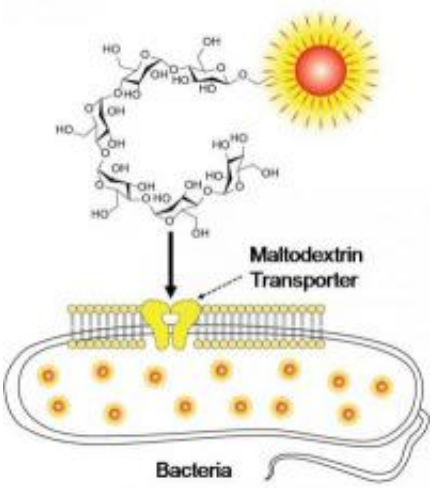

Schematic showing the chemical design of maltodextrin-based imaging probes, which have been used to detect bacterial infections in animals with high sensitivity and specificity. The probes are composed of maltohexaose conjugated to a fluorescent dye. They are internalized at a high rate by bacteria through the maltodextrin transport pathway as a glucose source. Credit: Georgia Tech/Niren Murthy

A new family of contrast agents that sneak into bacteria disguised as glucose food can detect bacterial infections in animals with high sensitivity and specificity. These agents -- called maltodextrin-based imaging probes -- can also distinguish a bacterial infection from other inflammatory conditions.

"These contrast agents fill the need for probes that can accurately image small numbers of bacteria in vivo and distinguish infections from other pathologies like cancer," said Niren Murthy, an associate professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "These probes could ultimately improve the diagnosis and treatment of bacterial infections, which remains a major challenge in medicine."

The imaging probes were described in the July 17, 2011 advance online edition of the journal Nature Materials.

Coulter Department postdoctoral fellows Xinghai Ning and Seungjun Lee led the project. University of Georgia Complex Carbohydrate Research Center postdoctoral associate Zhirui Wang; and Georgia State University Department of Biology associate professor Eric Gilbert and student Bryan Subblefield also contributed to the work.

In the United States in 2010, bacterial infections caused 40,000 deaths from sepsis and were the leading cause of limb amputations. A major limitation preventing the effective treatment of bacterial infections is an inability to detect them inside the body with accuracy and sensitivity. To image bacterial infections, probes must first deliver a large quantity of the contrast agent into bacteria.

"Most existing imaging probes target the bacterial cell wall and cannot access the inside of the bacteria, but maltodextrin-based imaging probes target a bacterial ingestion pathway, which allows the contrast agent to reach a high concentration within bacteria," said Murthy.

Maltodextrin-based imaging probes consist of a fluorescent dye linked to maltohexaose, which is a major source of glucose for bacteria. The probes deliver the contrast agent into bacteria through the organism's maltodextrin transporter, which only exists in bacterial cells and not

mammalian cells.

"To our knowledge, this represents the first demonstration of a targeting strategy that can deliver millimolar concentrations of an imaging probe within bacteria," noted Murthy.

In experiments using a rat model, the researchers found that the contrast agent accumulated in bacteria-infected tissues, but was efficiently cleared from uninfected tissues. They saw a 42-fold increase in fluorescence intensity between bacterial infected and uninfected tissues. However, the contrast agent did not accumulate in the healthy bacterial microflora located in the intestines. Because systemically administered glucose molecules cannot access the interior of the intestines, the bacteria located there never came into contact with the probe.

They also found that the probes could detect as few as one million viable bacteria cells. Current contrast agents for imaging bacteria require at least 100 million bacteria, according to the researchers.

In another experiment, the researchers found that the maltodextrin-based probes could distinguish between bacterial infections and inflammation with high specificity. Tissues infected with E. coli bacteria exhibited a 17-fold increase in fluorescence intensity when compared with inflamed tissues that were not infected.

Additional laboratory experiments showed that the probes could deliver large quantities of imaging probes to gram-positive and gram-negative bacteria for internalization. Both types of bacteria internalized the maltodextrin-based probes at a rate three orders of magnitude faster than mammalian cells.

"Maltodextrin-based probes show promise for imaging infections in a wide range of tissues, with an ability to detect bacteria in vivo with a

sensitivity two orders of magnitude higher than previously reported," said Murthy.

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