New 'interspecies communication' strategy between gut bacteria and mammalian hosts uncovered

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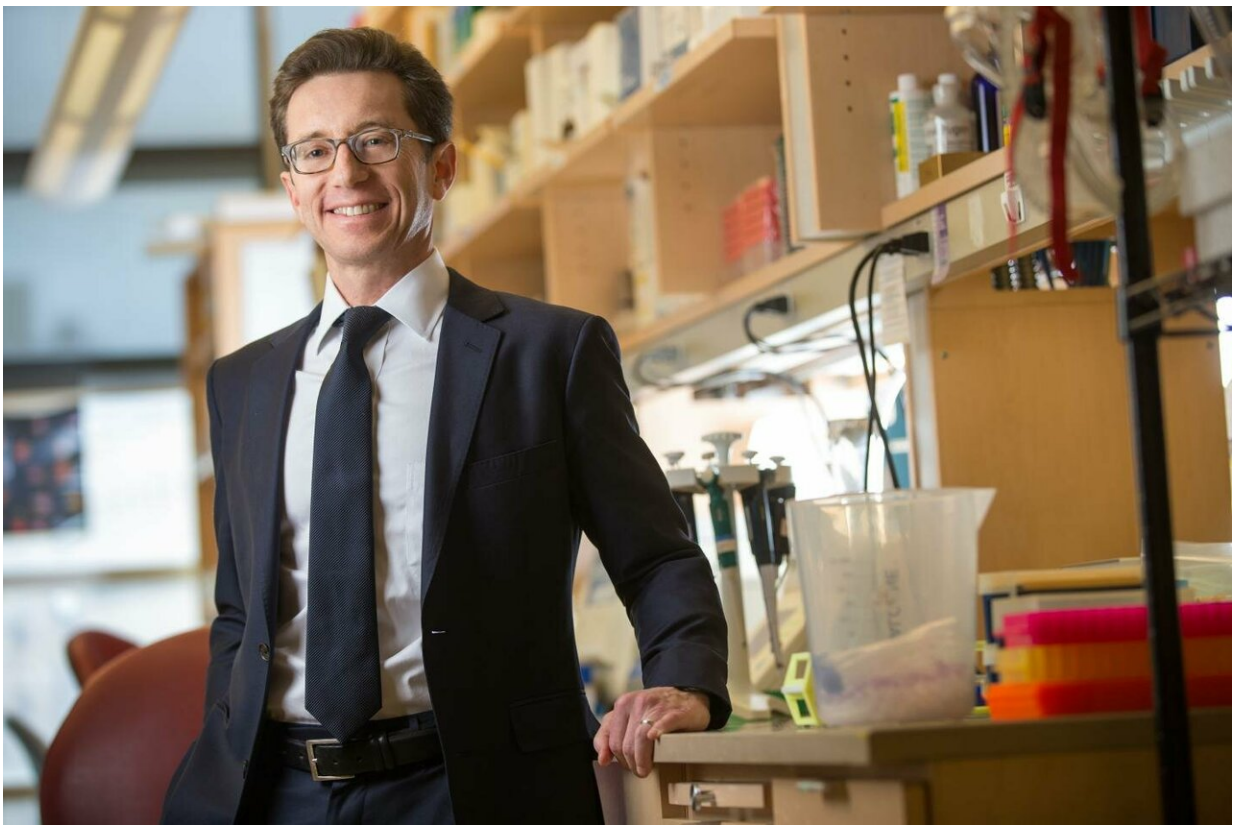

With trillions of bacteria in the average gut, researchers decided to look for a common language that all bacterial species might use. "There is tremendous complexity in the gut, and many researchers are after the next unusual substance produced by a bacterium that might affect human health. The enormity of the gut bacteria population and its relationship to the host predicts there will be general means to communicate that we humans can recognize." ~ Jonathan

Stamler, M.D. Credit: Case Western Reserve University School of Medicine

Bacteria in the gut do far more than help digest food in the stomachs of their hosts, they can also tell the genes in their mammalian hosts what to do.

A study published today in *Cell* describes a form of "interspecies communication" in which bacteria secrete a specific molecule—nitric oxide—that allows them to communicate with and control their hosts' DNA, and suggests that the conversation between the two may broadly influence human health.

The researchers out of Case Western Reserve University School of Medicine, University Hospitals Cleveland Medical Center, and Harvard Medical School tracked nitric oxide secreted by gut bacteria inside tiny worms (C. elegans, a common mammalian laboratory model). Nitric oxide secreted by gut bacteria attached to thousands of host proteins, completely changing a worm's ability to regulate its own gene expression.

The study is the first to show gut bacteria can tap into nitric oxide networks ubiquitous in mammals, including humans. Nitric oxide attaches to human proteins in a carefully regulated manner—a process known as S-nitrosylation—and disruptions are broadly implicated in diseases such as Alzheimer's, Parkinson's, asthma, diabetes, heart disease , and cancer.

The findings suggest nitric oxide is a general mechanism by which gut bacteria can communicate with mammalian hosts. Previous work to untangle communication lines to and from gut bacteria has primarily focused on rare molecules that bacteria secrete. The new findings are

akin to uncovering a chemical language common across species, as opposed to single words, said senior author Jonathan Stamler, MD, director of the Institute for Transformative Molecular Medicine at Case Western Reserve University School of Medicine and president of the Harrington Discovery Institute at University Hospitals Cleveland Medical Center. "There is tremendous complexity in the gut, and many researchers are after the next unusual substance produced by a bacterium that might affect human health," he says. With trillions of bacteria in the average gut, Stamler decided to look for a common language that all bacterial species might use. "The enormity of the gut bacteria population and its relationship to the host predicts there will be general means to communicate that we humans can recognize."

The researchers demonstrated the phenomenon by feeding developing worms bacteria that produce nitric oxide. They then selected one very important protein—argonaute protein, or ALG-1—that is highly conserved from worms to humans and silences unnecessary genes, including genes critical for development. When nitric oxide secreted by the bacteria attached to ALG-1, they developed malformed reproductive organs and died. Too much nitric oxide from bacteria commanded the worms' DNA silencing proteins and impaired healthy development.

"Practically, animals will not let this happen," Stamler said. Instead, the authors speculate a mammalian host outside of a laboratory setting will adjust to accommodate changing nitric oxide levels. Said Stamler, "The worm is going to be able to stop eating the bacteria that make the nitric oxide, or it will begin to eat different bacteria that makes less nitric oxide, or change its environment, or countless other adaptations. But by the same token, too much nitric oxide produced by our microbiome may cause disease or developmental problems in the fetus."

The study adds to a growing body of evidence that bacteria living in the gut, determined by diet and environment, have a tremendous influence

on mammalian health. Stamler imagines nitric oxide may represent an opportunity to manipulate this symbiotic relationship. Just as probiotics are designed to improve digestion, inoculating a person's gut with bacteria to improve nitric oxide signaling is conceivable. "I now think of this therapeutically, as a drug. There are tremendous opportunities to manipulate nitric oxide to improve human health."

While nitric oxide and S-nitrosylation may be a general mode of interspecies communication with broad health implications, it will require additional future research. Will nitric oxide be the only chemical communication channel? "We're basically seeing a new field opening for general strategies of communication," says Stamler. "There will be others."

More information: Puneet, S., et al. "Regulation of microRNA machinery and development by interspecies s-nitrosylation." *Cell*. DOI: 10.1016/j.cell.2019.01.037 , www.cell.com/cell/fulltext/S0092-8674(19)30100-X

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