New target found for nitric oxide's attack on salmonella bacteria

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A new target for nitric oxide has been revealed in studies of how it inhibits the growth of Salmonella. This bacterium is a common cause of food-poisoning.

"Nitric oxide is naturally produced in the nose and the gut and other tissues in the body to ward off infection," explained the senior author of the paper, Dr. Ferric Fang. He is a University of Washington (UW) professor of laboratory medicine, microbiology and medicine.

Nitric oxide – not to be confused with nitrous oxide, the laughing gas in dentists' offices – is similar to the preservatives in hotdogs, Fang said. Reactive nitrogen species, like nitric oxide, make brown meat an appetizing pink. They also weed out microorganisms that spoil food or cause food poisoning.

Fang's lab has made several important discoveries on ways mammals exploit the biochemical properties of nitric oxide to defend themselves from germs. Nitric oxide, a key actor in the body's innate immune defenses, apprehends a rogue's gallery of disease-causing organisms.

The newest results underscore that nitric oxide's antimicrobial actions are due to its interference with the metabolism, or energy production, of pathogens.

"Nitric oxide imposes substantial metabolic restrictions on bacteria," the researchers noted. Fang explained that its reactions with numerous

metabolic targets accounts for the broad-spectrum nature of its success. It keeps many types of disease-causing bacteria at bay. It also prevents an overgrowth of the body's many helpful bacteria.

The latest report on the versatility of nitric oxide in arming hosts against pathogens is published in the July 21 issue of *Cell Host & Microbe*. Dr. Anthony R. Richardson, who is now at the University of North Carolina at Chapel Hill, led the research while he was a postdoctoral fellow in the Fang lab.

Fang's team looked at the multi-pronged action of nitric oxide on Salmonella enterica serovar Typhimurium. This type of Salmonella can contaminate food and is similar to the bacteria that cause typhoid fever.

Nitric oxide and related chemicals put Salmonella into a difficult situation called nitrosative stress. When exposed to nitric oxide, Salmonella is unable to make two essential amino acids, methionine and lysine.

Without these, Salmonella cannot grow.

"This is bad news for the bacteria, but not for the host," Fang said. "Nitric oxide doesn't damage the host that produces it."

The ability to withstand nitrosative stress makes some forms of bacteria more virulent than milder types that can't handle it.

Richardson and his colleagues found that nitric oxide and its cousins throw a monkey wrench into several points in the Krebs cycle, also known as the tricarboxylic acid cycle. This cycle is the second stage in cellular respiration, when fuel is broken down to release energy for cell growth and division.

The researchers outlined how multiple interruptions in this cycle create a series of biochemical consequences that starve Salmonella of methionine and lysine. Nitric oxide also blocks certain regulatory genes that otherwise would give Salmonella an alternate chemical route out of its distress.

"Collectively, this work demonstrates that nitric oxide imposes substantial metabolic restrictions on bacteria," the authors concluded.

In a commentary on these findings, Dr. Stephen Spiro of the Department of Molecular and Cell Biology at the University of Texas at Dallas wrote that the work "focuses renewed interest in central metabolic pathways as nitric oxide targets."

"More generally," he noted, "this study provides an excellent illustration that a proper understanding of host-pathogen interactions and the development of therapeutic interventions require a detailed knowledge of pathogen metabolism."

Nitric oxide's targeting of the Krebs cycle is not unique to Salmonella. In learning how the body naturally controls the energy supplies and growth of varied disease-causing organisms, Fang said, scientists may be able to develop new broad-spectrum antimicrobials that mimic these effects, drugs that promote the body's own natural defenses against infection, or agents that overcome the ways virulent bacteria compensate when being starved of certain nutrients.

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