Bacterial resistance to copper in the making for thousands of years

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Low-temperature electron micrograph of a cluster of E. coli bacteria. Each individual bacterium is oblong shaped. Photo by Eric Erbe, digital colorization by Christopher Pooley.

Human use of copper dating back to the Bronze Age has shaped the evolution of bacteria, leading to bugs that are highly resistant to the metal's antibacterial properties.

Large amounts of copper are toxic to people and to most living cells. But our immune systems use some copper to fend off bacteria that could make us sick.

More copper in the environment leads to more bacteria, including *E. coli*, that develop a genetic resistance. And that could pose an increased infection risk for people, said Jason Slot, who directed a new copper-

resistance study and is assistant professor of plant pathology at The Ohio State University.

Today, copper is widely used, including in animal feed and to make hospital equipment - areas that could be particularly conducive to bacteria developing even greater resistance, Slot said.

Under the pressure of "copper stress," bacteria have traded DNA that enabled some to outlive the threat, said Slot, who specializes in fungal evolutionary genomics. And over centuries, the genes that lead to copper resistance have bonded, forging an especially tough opponent for the heavy metal, a cluster scientists call the "copper homeostasis and silver resistance island," or CHASRI.

Slot and his colleagues created a molecular clock, using bacterial samples collected over time and evolutionary analysis to trace the history of copper resistance. The team studied changes in bacteria and compared those to human use of copper. Their work suggests there were repeated episodes of genetic diversification within bacteria that appear to correspond to peaks in copper production.

The study appears in the journal *Genome Biology and Evolution*.

Slot, an evolutionary biologist, first became interested in copper resistance when he learned that the genes involved weren't evolving in the way scientists would expect.

"This may have arisen at the time that humans started using a lot of copper - in the Bronze Age," Slot said. He and his collaborators speculate that the original resistance might have started in milk fermented in a copper-alloy vessel, or in the gut of an animal in a high-copper environment.

From then on, human use of copper has likely contributed to bacteria with a stronger armor against it. For instance, "About 2,000 years ago Romans were pumping a ton of copper dust into the environment," Slot said. Ice cores from Greenland have supported this theory, showing likely high copper emissions during the time.

Today, copper is widely used in industry, including in farming, where the metal is added to feed to fatten up animals. And in recent years, there's been a movement toward using copper more in medical settings because of its antibacterial properties, Slot said.

"You're enticing the bacteria in the environment to develop a mechanism that evades your immune system," Slot said.

"I think overuse of anything is a bad idea, but it's really hard for people not to overuse the few weapons that we have."

Provided by The Ohio State University

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