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In a first-of-its-kind discovery, bacteria found to form potentially infective prions

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Nerve-damaging protein particles called prions have long been known to exist in mammals.

Now, in a surprising discovery, investigators from Harvard Medical School report they have found evidence that bacteria can also make prions.

Prions—self-propagating clumps of misfolded protein—have been identified as the cause of several rare but universally fatal neurodegenerative conditions, including bovine spongiform encephalopathy, popularly known as mad cow disease. While the most common cause of prion diseases in humans is consuming infected meat, some can be inherited or occur spontaneously.

The experiments, published online Jan. 13 in the journal *Science*, identified a protein with prion-forming potential in the bacterium Clostridium botulinum. However, the researchers say, many other bacteria—including those known to cause harm in humans as well as harmless and beneficial ones normally found in the human body—likely carry proteins with prion-forming potential.

Because the prion-forming protein identified in the study normally functions as a regulator of gene activity, the researchers say their discovery raises the possibility that when it switches to a prion state, it could alter genetic expression and bacterial behavior. Such changes, according to the investigators, could enhance bacterial survival under

challenging conditions and fuel bacterial fitness and diversity. In other words, bacterial prions, could boost bacteria's ability to cause disease, evade immune system surveillance and elude drugs.

"By switching certain genes on and off, prions could help bacteria survive environmental stresses rendering them less vulnerable to drugs, chemicals and other environmental assaults," says investigator Ann Hochschild, professor of microbiology and immunobiology at HMS.

Additionally, the researchers say, their findings suggest that prions are an ancient biologic phenomenon, emerging before primitive bacterial cells split from the more structurally complex cells that make up animals and plants some 2.3 billion years ago.

The defining characteristic of prions is their ability to induce properly folded, normally functioning proteins to contort and become misfolded. In other words, the researchers say, a prion provides a manual for other proteins to follow suit, unfolding and refolding, thus radically changing their normal structure and function. In mammals, the accumulation of these misshapen proteins leads to rapid cell demise in the brain. In fungi, however, prions do not cause damage but instead appear to confer beneficial traits to the cells that harbor them. Similarly, bacterial prions may help bacteria adapt to environmental challenges.

In the current study, scientists screened more than 60,000 bacterial genomes for the presence of proteins whose chemical makeup suggested they could be capable of forming prions. One such protein, called Rho factor, was detected in C. botulinum. Rho, found in many bacteria, acts as a protein regulator of bacterial gene expression, determining which genes get turned on or off.

In a series of experiments, the researchers demonstrated that in addition to its main role, Rho could also assume the behavioral characteristics of

a prion maker. Indeed, the experiments show that Rho can form telltale protein deposits called amyloids, the footprints of prion formation.

When the researchers inserted bacterial prions in yeast cells, the prions began self-propagating and multiplying, a sign of their infectivity. Furthermore, when the researchers introduced C. botulinum-derived prions into the lab-made form of the bacterium E. coli, the prions were, once again, capable of propagating inside the new organism.

"What we observed were the hallmarks of prion behavior—abilities to propagate and induce heritable changes in the structure and function of proteins in two model organisms," says study investigator Andy Yuan, a research fellow at HMS.

More information: Andy H. Yuan et al. A bacterial global regulator forms a prion, *Science* (2017). DOI: 10.1126/science.aai7776

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