Spore formation model could advance medicine

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Michigan State University scientists have produced experimental and modeling results that shed light on how a particular type of enzyme functions during spore formation, potentially advancing human health and disease research.

The work, published in the *Proceedings of the National Academy of Science*, may lead to new strategies to control formation of spores—highly resistant cells that promote persistence of some important human pathogens. This could have more far-reaching implications, as these enzymes are broadly conserved in almost all living organisms, including humans.

"The idea is that if you understand the sporulation process, then you might be able to devise ways to inhibit it or enhance it, because there are actually some good purposes spores serve," said Lee Kroos, a professor in the Department of Biochemistry and Molecular Biology in the MSU College of Natural Science and the study's senior author. "For instance, people are engineering spores to display things on their surface in order to make vaccines or something we can ingest, like a probiotic."

A group of enzymes, known as intramembrane proteases, or IMMPs, regulate diverse processes by cutting proteins within a cellular membrane or near the membrane surface. The research conducted by Kroos and the research team illuminates how the IMMP enzyme interacts with the protein it cuts during sporulation—the formation of dormant bacteria. The enzyme and protein are commonly found in spore-forming bacteria.

Understanding how the two proteins interact is the first step toward devising strategies to control spore formation.

"These IMMPs are like scissors in a membrane because they cut other proteins and release them from the membrane," said Kroos, who is also an MSU AgBioResearch scientist. "The proteins that they cut can be transcription factors—proteins that regulate other genes—for instance, to signal a change in temperature, and it's a way to communicate across a membrane."

Postdoc Sabyasachi Halder and graduate student Daniel Parrell in the Kroos group, along with Biochemistry and Molecular Biology colleague Michael Feig and Doug Whitten, proteomics facility director for the MSU Research Technology Support Facility, focused on a model for important pathogens such as the one that causes anthrax. Other cousins of B. subtilis, called Clostridia, cause illnesses such as tetanus and botulism.

"Spores are resting cells; they don't need food and they are very resistant to dryness, heat and UV light," Kroos said. "It's a way for cells to survive when conditions are bad. That's really important, because there are a number of pathogens that form spores and persist in the environment until a suitable host is present."

The model could help develop drugs that would inhibit or enhance these types of enzymes. The work has implications beyond sporulation, because the enzymes are found in humans and other animals, as well as in plants.

"We study the enzymes in bacteria because bacteria are easy to study, but we imagine some of the fundamental things that we learn will be found in the related enzymes in other organisms," Kroos said. "For example, in humans there is a related enzyme that is involved in the

expression of genes that control cholesterol and fatty acid metabolism and respond to certain kinds of stress that cause protein unfolding or inflammation."

More information: Sabyasachi Halder et al. Interaction of intramembrane metalloprotease SpoIVFB with substrate Pro-σK, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1711467114

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