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Study finds possible 'persistence' switch for tuberculosis

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(PhysOrg.com) -- An examination of a portion of the tuberculosis genome that responds to stress has allowed Rice University bioengineers Oleg Igoshin and Abhinav Tiwari to zero in on a network of genes that may "switch" the disease into dormancy.

The bacteria that cause tuberculosis (TB), Mycobacterium tuberculosis, can transition into a dormant state to ward off attacks from antibiotics and the immune system. A new report from Igoshin and Tiwari in this month's issue of *Physical Biology* examines a network of genes that may make this possible. A computer model of the network showed it can act as a "persistence" switch that toggles the organism from a fast-growing to a slow-growing state.

"The molecular mechanisms that allow Mycobacterium tuberculosis to switch into this slow-growing, persistent state have been associated with genes that are activated when the microorganism is under stress," said Igoshin, senior author of the study and an assistant professor in bioengineering at Rice.

Tiwari, lead author of the study and a graduate student in Igoshin's lab, said, "We examined a stress-response network of genes that are found in both the TB bacterium and other closely related mycobacteria. We analyzed the role of multiple feedback loops in this network, and were eventually able to identify an ultrasensitive mechanism that works in combination with the feedback loops to form a switch. This switch can possibly activate transition to the persistent state."

The study was a collaborative effort between Igoshin's laboratory at Rice's BioScience Research Collaborative and the research groups of Gabor Balazsi at the University of Texas M.D. Anderson Cancer Center and Maria Laura Gennaro at the Public Health Research Institute of the New Jersey Medical School.

Scientists have long known that the TB bacterium has the ability to "hunker down" and go dormant under stressful conditions. Previous studies have confirmed that both the slow-growing and fast-growing forms of the bacteria have identical genes.

"The fact that the same organism can exist in two states at the same time in the same environment raises many questions," Igoshin said. "What is the basis for this bistability? What are the environmental cues that activate the switch?"

Other bacteria can switch between stable states as well, but Mycobacterium tuberculosis' ability to make this transition is one reason TB is such a widespread disease. As much as 30 percent of the world's population is believed to be infected with TB, which causes about 2 million deaths every year.

Igoshin said advances in molecular microbiology have allowed researchers to identify networks of mycobacterial genes that become activated when the organism is stressed. One of these networks contains genes that make mycobacterial transcription factor (MprA) and another protein called sigma factor E (SigE).

"Our collaborative team developed an approach that allowed us to formulate general conclusions about the properties of the mycobacterial stress-response network, even though we had limited knowledge of the underlying parameter values," Igoshin said.

Tiwari said, "Using this approach, we systematically examined the different modules, or subsets, of the full network. We found that bistability was linked to a positive feedback loop between MprA and SigE, a protein that binds to RNA polymerase to promote the production of both MprA and SigE."

Igoshin and Tiwari believe their modular approach to investigate the role of multiple feedback loops could also be used to unravel mechanisms that other bacteria use to control bistability.

"There are many outstanding questions regarding the specific ways that gene regulatory networks operate in bacteria," Igoshin said. "The generality of this modular approach opens up a promising avenue for answering some of those questions because it can be readily adapted to other networks."

And that is precisely what Igoshin's lab and its collaborators are preparing to do thanks to a recently awarded five-year, $1.35 million grant from the National Institutes of Health (NIH).

"We want to understand -- at a network-level -- how different organisms mount these types of responses," Igoshin said. "We need this to better understand how cells function and to build better computer models of pathogenic bacteria that cannot be easily manipulated in the laboratory."

Provided by Rice University

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