New study examines how bacteria acquire immunity

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In a new study this week, Rice University scientists bring the latest tools of computational biology to bear in examining how the processes of natural selection and evolution influence the way bacteria acquire immunity from disease.

The study is available online from Physical Review Letters. It builds upon one of the major discoveries made possible by molecular genetics in the past decade -- the revelation that bacteria and similar single-celled organisms have an acquired immune system.

"From a purely scientific perspective, this research is teaching us things we couldn't have imagined just a few years ago, but there's an applied interest in this work as well," said Michael Deem, the John W. Cox Professor in Biochemical and Genetic Engineering and professor of physics and astronomy at Rice. "It is believed, for instance, that the bacterial immune system uses a process akin to RNA interference to silence the disease genes it recognizes, and biotechnology companies may find it useful to develop this as a tool for silencing particular genes."

The new study by Deem and graduate student Jiankui He focused on a portion of the bacterial genome called the "CRISPR," which stands for "clustered regularly interspaced short palindromic repeats." The CRISPR contain two types of DNA sequences. One type -- short, repeating patterns that first attracted scientific interest -- is what led to the CRISPR name. But scientists more recently learned that the second type -- originally thought of as DNA "spacers" between the repeats -- is what

the organism uses to recognize disease.

"Bacteria get attacked by viruses called phages, and the CRISPR contain genetic sequences from phages," Deem said. "The CRISPR system is both inheritable and programmable, meaning that some sequences may be there when the organism is first created, and new ones may also be added when new phages attack the organism during its life cycle."

The repeating sequences appear to be a kind of bookend or flag that the organism uses to determine where a snippet from a phage begins and ends. The CRISPR will often have between 30 and 50 of these snippets of phage sequences. Previous studies have found that once a bacteria has a phage sequence in its CRISPR, it has the ability to degrade any DNA or RNA that match that sequence -- meaning it can fend off attacks from any phages that have genes matching those in its CRISPR.

"What we wanted to explore was how the history of a bacterium's exposure to phages influences what's in the CRISPR," Deem said. "In other words, how is an organism's previous exposure to viruses reflected in its own genome?"

From earlier published studies, Deem and He knew that phage sequences were added to the CRISPR sequentially. So, in a CRISPR system containing 30 snippets, the newest one would be in position one, at the front of the line. In another study in 2007, researchers examining the CRISPR of whole populations of bacteria noticed some statistical irregularities. They found that the likelihood of two different organisms having the same snippet in their CRISPR increased exponentially as they progressed away from position one. So, in the organism with 30 snippets, the phage gene in position 30 was the most likely to be conserved time and again across all the bacteria in the population.

To use the power of computers to examine why this happens, Deem and

He needed a mathematical description of what was happening over time to both the bacterial and phage populations. The equations they created reflect the way the bacterial and phage populations interact via the CRISPR.

"Each population is trying to expand, and selective pressure is constantly being applied on both sides," Deem said. "You can see how this plays out in the CRISPR over time. There's a diverse assortment of genes in the first spacer, but the second spacer has been in there longer, so there's been more selective pressure applied to that spacer. Because bacteria that contain the dominant viral strain in their CRISPR are more likely to survive than those that don't, they tend to squeeze out their neighbors that are more vulnerable. At position N, the farthest way from position one, selection has been at work the longest, so the genes we find there were the most common and the ones that tended to afford the most overall protection to the organism."

In addition to interest from biotechnology firms, Deem said the workings of the CRISPR are of interest to drugmakers who are investigating new types of antibiotics.

Provided by Rice University