Evolution writ small: Study measures physical effects of evolution at molecular scale

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A unique experiment at Rice University that forces bacteria into a head-to-head competition for evolutionary dominance has yielded new insights about the way Darwinian selection plays out at the molecular level. An exacting new analysis of the experiment has revealed precisely how specific genetic mutations impart a physical edge in the competition for survival.

The new research, which could lead to more effective strategies to combat antibiotic drug resistance, was the most downloaded article this month in the journal *Molecular Systems Biology*.

The research builds upon an ingenious 2005 study involving bacteria called "thermophiles," which thrive at high temperatures. Researchers in the laboratory of Rice biochemist Yousif Shamoo "knocked out" a key gene that allowed the thermophiles to make energy at high temperatures. These crippled versions of the bacteria were then grown inside fermentors for several weeks. Each day, the temperature of the fermentors was increased. As a result, the bacteria were forced to either starve or adapt to survive at high temperature.

Of the hundreds of possible mutations, only five proved successful in allowing the cells to adapt and survive at high temperature. Each of these had mutations in a gene that creates a key enzyme that helps make energy at high temperature. Each of the five made a slightly different

version of the enzyme.

"One of these five eventually won out entirely and drove all the others to extinction," said Shamoo, associate professor of biochemistry and cell biology and director of Rice's Institute of Biosciences and Bioengineering. "The question is what physical advantage did that particular mutant have? What were the precise physical changes to the enzyme that allowed that strain to outcompete its cousins?"

Finding the answer to that question was painstaking. While the genetic mutations were known from the earlier study, it fell to graduate student Matt Peña to find out how small changes in the DNA structure of the bacteria translated into specific enzymatic changes. He found that adaptation depended critically on simultaneously keeping the enzyme working while also increasing its resistance to inactivation as the temperatures increased.

He found that versions of the enzyme -- which is a specific kind of protein -- that became inactive were also subject to protein misfolding. In humans, an inability to maintain properly folded and active proteins has been linked to several human diseases, including Alzheimer's.

"Studies like this can help us understand the physical basis for these kinds of diseases, and they can give us a better understanding for the molecular basis for adaptation," Shamoo said. "For example, what we learn from these thermophiles carries over into our work on drug-resistant bacteria because the principles of adaptation are the same no matter whether you're studying temperature, pH, antibiotic resistance or whatever," he said.

Shamoo's lab won funding from the National Institutes of Health in 2009 to study how bacteria evolve antibiotic resistance. One of the ultimate goals of the project is to predict how evolution will play out so that

drugmakers can head off resistance before it arises.

"With the thermophile study we've shown that it is possible to build a fitness function -- a mathematical expression -- that translates enzyme performance into a specific measure of competitive advantage," Shamoo said. "That's important because if you can't do that for one protein of interest, then there's no way you're going to be able to do it for a more complicated problem like antibiotic resistance, which involves simultaneous mutations to more than one gene."

Provided by Rice University