Cells that work hard stay alive, lazy cells die

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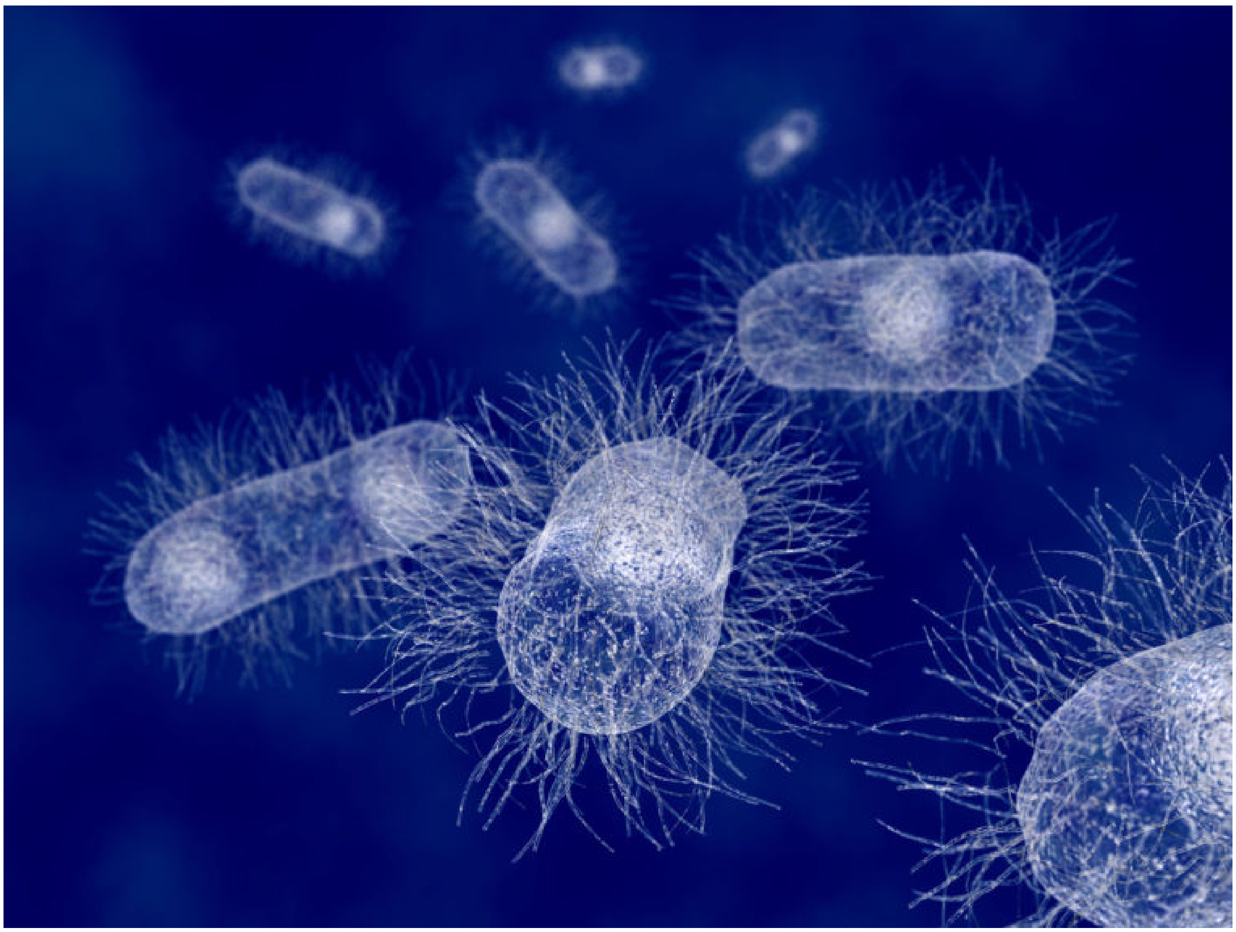

Engineered strains of E. coli were used in the cellular kill switch research. The PopQC sensor rewarded high-performing bacteria with extra protein to grow and thrive; the lazy bacteria were eliminated.

A team of engineers at Washington University in St. Louis discovered a way to improve production of biofuels, pharmaceuticals, materials and other useful chemicals by capitalizing on the work ethic of cells.

The research team, led by Fuzhong Zhang, assistant professor of energy, environmental & chemical engineering in the School of Engineering & Applied Science, discovered that genetically identical microbial cells have different work ethics. The team developed a tool to ensure that the hard-working cells keep working hard and the low-performing cells are eliminated.

The research is published online in *Nature Chemical Biology* March 21.

When engineering microbes to produce useful chemicals, cells from the same ancestor often perform tasks differently. Using engineered strains of the bacteria E. coli, Zhang's team demonstrated that only a small fraction of cells worked hard to produce the desired chemicals, while the majority of others were content to not work, but to eat nutrients intended for working cells. The different work ethic is not caused by unintended genetic mutations, they found, but rather by "noise" in biology, which is inherent in nature and impossible to eliminate.

To prevent the lazy cells from wasting nutrients, Zhang's team developed a quality-control tool, called PopQC, that can keep the hard-working, high-performing cells working while eliminating the low-performing cells. The team placed a sensor inside the cells that could sense how much work each cell was doing. If the sensor determined that a cell was making a lot of the products, the sensor would trigger a controller to make a protein that allowed the cells to survive and grow. If the sensor determined that the cell was not working hard enough, it remained silent, and the lazy cells died from lack of nutrition or were knocked out by antibiotics.

The team applied PopQC to two engineered strains of E. coli: one designed to produce free fatty acid, a precursor for biofuels or other high-volume chemicals; and one designed to produce tyrosine, an amino acid that can be a precursor to pharmaceuticals. PopQC allowed the hard-working cells to dominate in both cultures and led to threefold enhanced ensemble production of both free fatty acid and tyrosine, Zhang said.

"PopQC could be applied to a variety of biosynthetic pathways and host organisms as long as a proper sensor exists that detects the product in the engineered host," Zhang said. "Because noise is a universal problem in biology, the design principle of this work should inspire engineers from many other fields to improve efficiency of engineered systems."

Zhang has filed a patent application for the design principle with assistance from the university's Office of Technology Management.

Zhang's research interests focus on applying synthetic biology methodologies to develop microbial systems for the sustainable production of biofuels, chemicals and materials with defined structures and controllable properties. He also is interested in developing tools that allow engineered microbes to synthesize target products and to perform complex tasks more efficiently and robustly.

More information: Exploiting non-genetic cell-to-cell variation for enhanced biosynthesis, DOI: 10.1038/nchembio.2046

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