MAGIC system allows researchers to modulate the activity of genes acting in concert

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Genomic research has unlocked the capability to edit the genomes of living cells; yet so far, the effects of such changes must be examined in isolation. In contrast, the complex traits that are of interest in both fundamental and applied research, such as those related to microbial biofuel production, involve many genes acting in concert. A newly developed system will now allow researchers to fine-tune the activity of multiple genes simultaneously.

Huimin Zhao, Steven L. Miller Chair Professor of Chemical and Biomolecular Engineering at the University of Illinois, led the study. Zhao and his research team described their new functional genomics system, which they named multi-functional genome-wide CRISPR (MAGIC), in a recent publication in *Nature Communications*.

"Using MAGIC, we can modulate almost all ~6000 genes in the entire yeast genome individually or in combination to various expression levels," Zhao said. Zhao leads an interdisciplinary research group at Illinois' Carl R. Woese Institute for Genomic Biology (IGB) that aims to develop sophisticated synthetic biology tools to support biological systems engineering; MAGIC is one of the latest steps in streamlining such work in yeast.

The C in MAGIC stands for CRISPR, the acronymic that has come to stand for a type of molecular system used to edit DNA. The full name, Clustered Regularly Interspaced Short Palindromic Repeats, refers to DNA sequences that enable bacteria to protect themselves from viruses. Key sections of these sequences help specialized molecules produced by the bacteria to recognize and slice up viral genomes, effectively disabling them.

Researchers design their own DNA sequences that work within CRISPR systems to precisely edit the genomes of living things. The molecules originally borrowed from bacteria have been tweaked so that they can have one of several effects on the gene toward which they are targeted, either increasing, decreasing, or completely eliminating gene activity, according to the way that cuts in the genome are made and repaired.

Until now, though, there has been no easy way to use more than one of these editing modes simultaneously. Researchers could explore the effects of different changes but could not easily combine them, as if playing improv in a jazz trio in which only one instrument could be playing at any given time.

"We have developed the tri-functional CRISPR system which can be used to engineer the expression of specific genes to various expression levels," Zhao said. In other words, MAGIC allows researchers to bring two or all three instruments into the music session at once. When combined with the comprehensive "library" of custom DNA sequences created in Zhao's lab, his group can explore the effects of turning up, turning down, and turning off any combination of genes in the yeast genome simultaneously.

Exploring this genomic harmonizing, the synergistic effects of multiple simultaneous edits, will allow researchers to better understand and to enhance complex traits and behaviors of useful microorganisms. For example, Zhao's group used the MAGIC system to look for combinations of edits that helped their yeast strain tolerate the presence of furfural, a byproduct of cellulosic hydrolysates that can limit the survival and activity of yeast cells used for cellulosic biofuels production. The resulting engineered furfural tolerant yeast strain could produce more biofuels than the parent yeast strain in fermentation.

Zhao and his group introduced sequences from their MAGIC library into yeast and looked for yeast cells that could withstand high levels of furfural. They found that some of surviving cells had taken in MAGIC sequences that altered the activity of genes known to be involved in tolerating furfural; the involvement of other genes was discovered for the first time by this experiment. The team was able to integrate one of these effective MAGIC sequences into the yeast genomic DNA and then test how further sequences might enhance tolerance.

"We were most excited about the ability of MAGIC to identify novel genetic determinants and their synergistic interactions in improving a complex phenotype [like furfural tolerance], particularly when these targets must be regulated to different expression levels," Zhao said. Because MAGIC allows researchers to examine how different genetic changes might work in combination to produce an effect, the new system can lead to clearer analyses of how different biological processes are involved in a trait.

Zhao said that among several technical challenges of the work was the development of a screening method that could be carried out efficiently at a large scale, a capability he hopes to expand to other scientific questions and other organisms.

"These challenges should be addressed in order to apply MAGIC to other eukaryotic systems such as industrial yeast strains and mammalian cells," he said.

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