

Researchers build a toolbox for synthetic biology

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For about a dozen years, synthetic biologists have been working on ways to design genetic circuits to perform novel functions such as manufacturing new drugs, producing fuel or even programming the suicide of cancer cells.

Achieving these complex functions requires controlling many genetic and cellular components, including not only genes but also the regulatory proteins that turn them on and off. In a living cell, proteins called transcription factors often regulate that process.

So far, most researchers have designed their synthetic circuits using transcription factors found in bacteria. However, these don't always translate well to nonbacterial cells and can be a challenge to scale, making it harder to create complex circuits, says Timothy Lu, assistant professor of electrical engineering and computer science and a member of MIT's Research Laboratory of Electronics.

Lu and his colleagues at Boston University (BU), Harvard Medical School and Massachusetts General Hospital (MGH) have now come up with a new method to design transcription factors for nonbacterial cells (in this case, yeast cells). Their initial library of 19 new transcription factors should help overcome the existing bottleneck that has limited synthetic biology applications, Lu says.

The project is part of a larger, ongoing effort to develop genetic "parts" that can be assembled into circuits to achieve specific functions. Through this endeavor, Lu and his colleagues hope to make it easier to develop circuits that do exactly what a researcher wants.

"If you look at a parts registry, a lot of these parts come from a hodgepodge of different organisms. You put them together into your organism of choice and hope that it works," says Lu, corresponding author of a paper describing the new transcription factor design technique in the Aug. 3 issue of the journal *Cell*.

Lead authors of the paper include Ahmad Khalil, assistant professor of biomedical engineering at BU, Lu, and BU postdoc Caleb Bashor. Other authors are Harvard grad student Cherie Ramirez; BU research assistant Nora Pyenson; Keith Joung, associate chief of pathology for research at MGH; and James Collins, BU professor of biomedical engineering.

Binding DNA

Recent advances in designing proteins that bind to DNA gave the researchers the boost they needed to start building a new library of transcription factors.

Transcription factors include a section that recognizes and latches on to a specific DNA sequence called a promoter. The protein then recruits an enzyme called RNA

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polymerase, which starts copying the gene into messenger RNA, the molecule that carries genetic instructions to the rest of the cell.

In many transcription factors, the DNA-binding section consists of proteins known as zinc fingers, which target different DNA sequences depending on their structure. The researchers based their new zinc fingers designs on the structure of a naturally occurring zinc finger protein. "By modifying specific amino acids within that zinc finger, you can get them to bind with new target sequences," Lu says.

The researchers attached the new zinc fingers to existing activator segments, allowing them to create many combinations of varying strength and specificity. They also designed transcription factors that work together, so that a gene can only be turned on if the factors bind each other.

Andrew Ellington, a professor of biochemistry at the University of Texas at Austin, says the work is an important step toward creating more complex circuits in nonbacterial cells. "They've created a bunch of new transcription factors, and they've done it in a modular way, creating additional tools people can use to fashion new circuitry," says Ellington, who was not part of the research team.

Toward greater complexity

Such transcription factors should make it easier for synthetic biologists to design circuits to perform tasks such as sensing a cell's environmental conditions.

In this paper, the researchers built some simple circuits in yeast, but they plan to develop more complex circuits in future studies. "We didn't build a massive 10- or 15-transcription factor circuit, but that's something that we're definitely planning to do down the road," Lu says. "We want to see how far we can scale the type of circuits we can build out of this framework."

Synthetic biology circuits can be analog or digital, just like electrical circuits. Digital circuits include logic functions such as AND and OR gates, which allow cells to make unequivocal decisions such as whether to undergo programmed cell suicide. Analog functions are useful for sensors that take continuous measurements of a specific molecule in the cell or its environment. By combining those circuits, researchers can create more complex systems in which a digital decision is triggered once the sensor reaches a certain threshold.

In addition to building more complex circuits, the researchers are planning to try their new transcription factors in other species of yeast, and eventually in mammalian cells, including human cells. "What we're really hoping at the end of the day is that yeast are a good launching pad for designing those circuits," Lu says. "Working on mammalian cells is slower and more tedious, so if we can build verified circuits and parts in yeast and then import them over, that would be the ideal situation. But we haven't proven that we can do that yet."

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