

Rewriting the Story About the Molecules That Turn Genes On and Off

Fred Hutch researchers discover that most transcription factors in budding yeast don't follow the textbook example of binding close to the genes they regulate.

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Some things just go together like “rock and roll” and “fish and chips” or, in molecular biology, “transcription factors” and the “nearby genes they regulate.”

The standard, simplified story goes like this: transcription factors are molecular workers that scan DNA strands and bind to specific sequences close to the genes they either turn on or off.

When transcription factors find their target binding sites, they either initiate the genetic copying process that makes life's machinery, or they block it. Find a gene and there should be a binding site nearby for its transcription factor. Find a transcription factor, and there should be a gene nearby that it regulates.

It's an important story because poorly regulated transcription factors play a big role in the development and progression of cancer.

But a new study by researchers at Fred Hutch Cancer Center [published April 16 in Nature](#) introduces a major plot twist: the standard story is true only for a small subset of the transcription factors they mapped in budding yeast, a model organism commonly studied to understand fundamental biology.

Most transcription factors are not linked to a nearby target gene like peanut butter and jelly.

And rather than performing specialized tasks such as turning genes on or off, most transcription factors can do both jobs as well as other regulatory functions.

The findings were so unexpected that Lakshmi Mahendrawada, PhD, the study's lead author, thought she'd made a mistake.

“I questioned many times that we were doing something wrong because this is not what I read in the textbook,” said Mahendrawada, a postdoctoral researcher in the lab of transcription expert [Steven Hahn, PhD](#). “But after studying so many factors now, I'm very confident that whatever we

found is true.”

Swapping a fishing pole for a wide net

Hahn joined the [Basic Sciences Division](#) of Fred Hutch in 1988 and [built a career](#) as a leading biochemist specializing in the process that copies and transmits information from genes needed to make proteins, the cell’s various molecular workers.

For the last decade, his lab has focused on transcription factors in budding yeast that initiate that process by activating their target genes. It’s a complex problem because genes can be associated with more than one transcription factor, and transcription factors can target more than one gene.

Mahendrawada, a cell biologist by training, joined Hahn’s lab in 2019. Initially, she set out to understand how transcription factors in budding yeast work at different classes of genes.

But it was difficult to find variation. Studying transcription factors one at a time was like dropping a line in Lake Washington with its dozens of species of fish and hooking one yellow perch after another.

“Before Lakshmi came to the lab, we were getting frustrated because we kept finding the same kind of transcription activator over and over again, Hahn said. “But we were only looking at a small number, one at a time. So instead of pulling out one fish at a time, Lakshmi is very ambitious, and she said, ‘Let’s just look at everything all at once and see what happens.’”

She and Hahn and Linda Warfield, a research tech in the lab, conducted a comprehensive survey, mapping both the DNA locations and gene targets for 126 transcription factors, the nearly complete set for budding yeast.

Making a convincing case

To make the map, they used [a technique](#) well suited for budding yeast called ChEC-seq, [first developed](#) by their Basic Sciences Division colleague [Steven Henikoff, PhD](#), in 2015.

They fused the transcription factors with an enzyme activated by calcium that cuts the DNA into manageable bits precisely where the transcription factor attaches.

Then they analyzed the DNA sequences of those bits to map where all the transcription factors attach.

They found instances where a transcription factor binds to DNA and regulates the nearby gene, just like the standard story says it should, but they found many more examples where it didn’t work that way at all.

They discovered that contrary to expectations, the presence of a transcription factor binding to

DNA near a gene is not a good predictor of whether that factor regulates the gene.

It was an astonishing plot twist: Suddenly rock no longer went with roll and peanut butter might be missing jelly.

But Hahn knew they were onto something when they didn't find much of an overlap between all the places on DNA where transcription factors bind and the location of all the genes that transcription factors regulate.

If the standard story were true for all transcription factors, then they should have seen a much tighter overlap.

Instead, they found transcription factors that weren't located near the gene they were supposed to regulate, so it wasn't obvious why they were parked there.

And they found genes that didn't have their expected transcription factors nearby, which meant something else was regulating them.

And while they found some specialist transcription factors that either turn genes on or off in accordance with the standard story, most can do both and it isn't clear what triggers either function.

"That's one of the advantages of doing a large-scale screen like Lakshmi did instead of focusing on a few things that work," Hahn said. "You can get the bigger picture of how everything works."

The results were so unexpected that reviewers for Nature asked the team to do more experiments to make sure they weren't missing something.

"They were tough but fair for the most part, and they really pushed us," Hahn said. "The paper ended up being a lot better because they asked us to do all these controls and extensions of what we had done. And I think in the end what you want as a scientist, when you publish your results, is that it will be convincing to most people."

New questions and directions

If the standard story is true only for a small subset of transcription factors and the genes they regulate, then what the fish-and-chips is going on with the rest of them?

"Why are the factors binding but not regulating?" Hahn asked. "In another aspect, we have genes that are regulated, but we can't detect binding of the factor anywhere nearby. What's different about the genes where the factor does regulate it versus the ones where it doesn't regulate it? Those are the kinds of things in the future we would like to know."

Meanwhile, Hahn has discovered that they weren't the only ones in the field who noticed the mismatch between transcription binding and gene regulation.

“Once I started talking about this at seminars, people said, ‘Oh yeah, I got the same result. I see binding somewhere, but the genes aren’t regulated,’” Hahn said. “People have these anecdotes, but it’s kind of easier to go with the flow rather than contradict everything because it takes a lot more evidence than originally was required to come up with the model in the first place. The reality is more complicated than we thought.”

Their discovery has opened new research possibilities.

“We used to be a biochemical lab, but because of results like Lakshmi and Linda found in the lab, we’ve changed our direction as to what we’re going to work on in the future because this seems really exciting and really important to follow up on it,” Hahn said.

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