Transcription factors don't act like an 'on-off' switch, exhibit more complex binding behavior: study

April 11 2012

Anyone who's tried a weekend home improvement project knows that to do a job right, you've got to have the right tools. For cells, these "tools" are proteins encoded by genes. The right genes for the job are turned on only in the specific cells where they are needed. And every cell in your body has a specific job to do. Cells in your pancreas have to produce insulin, while cells in the retina of your eye must be able to sense light and color. Like using the wrong tool for the job, if the wrong genes are turned on in a cell, it can cause a real mess. Worse, in some cases it can cause serious disease like cancer.

Scientists have known this for decades. They've also known that there are specific proteins called "transcription factors" that control which genes are turned on or off in cells by binding to nearby DNA. Transcription factors were thought to act like a switch; they are either "on" (bound to DNA) or "off" (not bound).

A UNC-led team of scientists has now shown that transcription factors don't act like an 'on-off' switch, but instead can exhibit much more complex binding behavior.

"This is a new way of looking at how genes are controlled," says Jason Lieb, PhD, study senior author. "For a while now there have been molecular maps that show the location of where the proteins are bound to DNA – like a roadmap. For the first time, we are able to show the

molecular equivalent of a real-time traffic report." Their study appears in the April 12, 2012 issue of the journal *Nature*. Lieb is a professor of biology and a member of UNC Lineberger Comprehensive Cancer Center.

Working in yeast, the UNC team learned that the transcription factors' binding process is dynamic and involves more than just being bound or unbound. In addition to a stable binding state (on or off), the team demonstrates a state that they call "treadmilling," where no forward transcription process is occurring. Within this process, they hypothesize the existence of a molecular "clutch" that converts treadmilling to a stable bound state, moving the transcription process forward to completion to turn the gene on.

Lieb explains, "This discovery is exciting because we developed a new way to measure and calculate how long a protein is associated with all of the different genes it regulates. This is important because it represents a new step in the process of how genes are regulated. And with every new step, there are opportunities for new mechanisms of regulation." Lieb is director of the Carolina Center for Genome Sciences.

He adds, "We found that proteins that bind in the stable state are associated with high levels of gene transcription. We think that if we can regulate the transition between treadmilling and stable binding, we can regulate the outcome in terms of gene expression. Ultimately, this type of regulation could be important for genetic medicine – a new way to regulate the 'switches' that turn gene expression associated with disease on or off."

The team set up a controlled competition between two copies of the same transcription factor, each with a unique molecular tag. They let one of the proteins bind to all of its gene targets, then introduced the second copy. Next the team measured how long it took the competitor

transcription factor to replace the resident protein and used this data to calculate the residence time at each location in the genome. Colin Lickwar, MS, first author of the paper, says, "We didn't know if the residence time was important, but we found that the residence time was a much better indicator of whether a gene was turned on or off than previous measures of binding."

Anthony Carter, PhD, who oversees gene regulation grants at the National Institutes of Health's National Institute of General Medical Sciences, explains, "By taking an interdisciplinary approach that incorporates the use of mathematical modeling tools, Dr. Lieb has shed new light on a fundamental cellular process, the ability to quickly shift between active and inactive states of gene expression. The findings may offer new insights on how cells respond to developmental cues and how they adapt to changing environmental conditions." The National Institute of General Medical Sciences partially supported the work.

Provided by University of North Carolina School of Medicine