Scientists Pinpoint Protein's Role in Critical Gene Expression

UNC School of Medicine researchers led by Brian Strahl, PhD, and Jibo Zhang detail how a newly defined domain in a protein regulates gene expression, and how cells compensate when this normal process is disrupted. These insights have implications for cancer research.

CHAPEL HILL, NC – Each cell in our body needs a fuel source to grow and divide to keep us alive. Most cells prefer a fuel source of high energy-containing sugar, but there are many times when our cells find themselves in short supply and must find other sources of energy to maintain their basic functions to stay alive. As most organisms experience times of feast and famine, cells have evolved ways to respond rapidly to a changing nutrient environment. The lab of Brian Strahl, PhD, interim chair of the UNC Department of Biochemistry and Biophysics at the UNC School of Medicine has unraveled more details for how cells do this, garnering insights into the basic ways in which cell epigenetics affect biology and disease.

The research, published in Genes & Development, has implications for cancer research because it explains part of the paradox for how cells can transcribe genes in the absence of high-energy sources, a situation that unfolds in cancer and has puzzled researchers for years.

In the case of when cells have high amounts of energy, organisms make high-energy molecules that fuel cell growth and division. In fact, a property of cancer cells is having access to high amounts of sugar to feed cancer growth. In contrast, when cells run out of these "preferred" energy sources, they will turn to other ways (or metabolic systems) to create energy to stay alive. As is the case in dieting, cells will break down fats in times of fasting. Cells are well equipped to deal with changing nutrient environments.

"But how cells adapt to these changes and initiate their specialized gene expression programs to handle the new jobs created by the cell under nutrient flux is one of the big mysteries in the field," said Strahl, senior author of the paper and Oliver Smithies Investigator at UNC-Chapel Hill. To investigate how cells do this, Strahl's lab applied a specialized lab system that allowed them to grow a naturally occurring yeast in a chamber where they could precisely control the available energy sources. In doing so, they were able to force yeast to go through waves of feast and famine that they could easily study. The waves of feast and famine lead to waves of metabolic change, which allowed the researchers to examine the details of what happened at the gene level.

All cells have the same genetic information or blue print of life but use this information differently in order to create specialized functions – for example, to create different cell types or tissues – and to even handle changes to the environment, such as energy flux. Decades of research have revealed that the way different genes can be activated within the genomic blueprint is through small chemical additions (or molecular tags) to proteins called histones that wrap up our DNA. The chemical signals or tags help to push the DNA to "open up" and turn a gene on or "close down" and turn a gene off. Yet, how changes in

nutrient availably were able to “speak” to the genome to instruct change in gene expression was poorly understood.

Using yeast as a model, Strahl lab graduate student Jibo Zhang led experiments showing that under times of high energy, a byproduct from metabolism helps drive up the levels of one molecular tag on the histones. This process is called acetylation. In doing so, the researchers found that a newly identified domain in a protein that regulates the expression of a gene called Yaf9 could bind this tag and bring with it much of the machinery to create gene expression. However, during times of fasting, the situation became much different. The high energy tag on the histones was taken away to create critically needed energy for the cells.

But Zhang also found that the recruitment of Yaf9 was also gone. Although this loss is normally thought to turn genes off, Zhang found that these times were in fact high in the enzymes that drive gene expression. Thus, cells found a way to still make gene expression happen under low nutrient conditions to address the need for gene expression without needing the high energy histone tag.

This shows that cells have evolved a way to make sure gene expression is still efficient at all times.

“We think the unique differences in the types of tags found between the two nutrient states (high versus low) may in fact be a special type of signal that makes sure gene expression programs are still efficient at both times,” said Zhang, first author of the paper.

This work has important implications for normal human biology and disease, such as cancer. It is well known that cancer cells require high energy sugars to maintain their growth and division. Much of cancer growth is metabolically driven.

The work from Strahl’s lab provides new insights into the process of how gene expression occurs under high energy conditions, which may open up new therapeutic targets and ways to intervene to disrupt cancer growth.

Co-author of the Genes & Development paper is Aakanksha Gundu, an undergraduate student at UNC-Chapel Hill. Brian Strahl is a member of the UNC Lineberger Comprehensive Cancer Center.

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