Chemical tags likely to affect metabolism, cancer development

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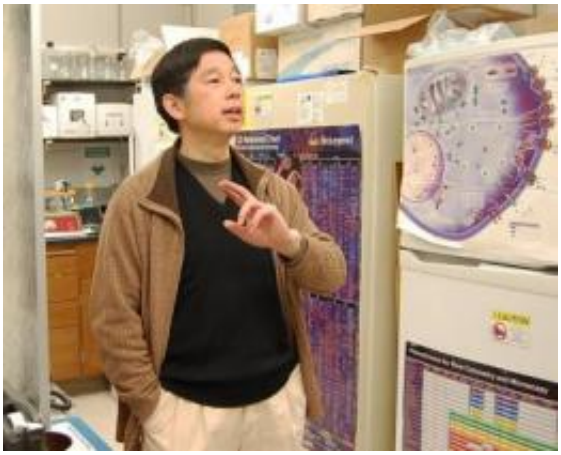

This is Yue Xiong, Ph.D., of University of North Carolina School of Medicine. Credit: UNC Medical Center News Office

It is not unusual to hear people blame their metabolism after gaining a few pounds. But changes in metabolism - the process that shapes how our bodies turn food into energy -- can have much more sinister effects than making it hard to fit into your favorite jeans.

In fact, differences in metabolic rates are known to exist between normal cells and tumor cells, though the mechanism behind it is unclear. Now new research from the University of North Carolina at Chapel Hill suggests that the addition or removal of a certain type of chemical tag - called an acetyl group - onto metabolic enzymes plays a key role in how

cellular metabolism is regulated.

The finding, which will appear in the February 19 issue of the journal *Science*, gives researchers vital clues to understand how normal cells respond to nutrient changes and how the process by which normal cells turn cancerous, and could one day lead to new drugs that starve cancer cells into submission.

"We have discovered an entirely new layer of control of metabolism," said Yue Xiong, Ph.D., professor of biochemistry and biophysics and a member of the UNC Lineberger Comprehensive Cancer Center. "This process -- the acetylation of metabolic enzymes -- appears to be highly conserved during evolution and very dynamic, which makes it an ideal target for future drug development. Now if we can identify which enzyme or enzymes are responsible for the difference in metabolism between normal and tumor cells, then we could have new targets for the treating cancer patients."

Xiong is a senior author of the study along with Kun-Liang Guan, professor of pharmacology, at the University of California, San Diego.

Almost all previous studies on acetylation have focused on the proteins in the nucleus, where acetyl tags regulate how tightly the DNA's genetic code is packaged. But Xiong and Guan started this study with the hypothesis that acetylation must also play a role in the other half of the cell, the cytoplasm.

So they separated the nucleus and the cytoplasm of primary liver cells, and then took a chemical census of the cytoplasm's contents using a technology called mass spectroscopy. They identified approximately a thousand new proteins that are acetylated, greatly expanding the previously recognized repertoire of fifty.

At first, the researchers were overwhelmed by such a large number of proteins to study, said Xiong. But then they began notice a pattern -- almost every metabolic enzyme was acetylated, presumably because their starting material was liver, an organ rich in metabolic activity.

"We think that acetylation is likely to play a very extensive role in regulation of many different cellular processes, not just metabolism," said Xiong.

Xiong and his colleagues looked at the acetylation of one enzyme from each of the four major metabolic pathways. They found that by altering the metabolic fuels that feed into these pathways they could alter the level of acetylation.

In addition, the researchers discovered that blocking acetylation chemically or genetically affected these metabolic enzymes in a number of different ways, either by stimulating its activity, inhibiting it, or degrading the protein itself. They suspect that acetylation is important for coordinating not only the players within a metabolic pathway but also between different pathways.

The next step is to take their finding in normal cells and see how it can inform their study of tumor cells. The researchers are in the process of looking at each metabolic enzyme, one-by-one, to see which one displays the most disparate acetylation patterns between normal and cancer cells. They will then try to use the very same proteins that tack on or pull off those acetyl groups - called acetylases or deacetylases, respectively -- to modify acetylation and thwart cancer development.

Provided by University of North Carolina School of Medicine

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