Cell stress response and fat and obesity gene linked

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In one fell swoop, Cornell researchers have discovered mechanisms that control the function of a fat and obesity gene while at the same time answering a long-standing question about how cells respond to stress.

The research, published in the journal *Nature* Oct. 22, focuses on heat shock genes, which are found in cells of many organisms and become activated when temperatures rise above a threshold. For example, heat shock genes in fruit flies will activate on hot days, and in humans, when they have fevers.

The genes express heat shock proteins, which protect essential cell proteins and remove damaged proteins before they accumulate and lead to dysfunction, disease and cell death.

"Heat shock genes and their heat shock proteins are highly expressed during stress and are very critical to protect cells; without them cells would quickly die under stress," said Shu-Bing Qian, associate professor of nutritional sciences, and the paper's senior author, along with Dr. Samie Jaffrey, professor of pharmacology at Weill Cornell Medicine. Jun Zhou, a postdoctoral research associate in Qian's lab, is the paper's first author.

The process of making heat shock proteins is not simple, because when cells heat up, their protein-making machinery shuts down. This pause in function protects the cell from making proteins at a time when they are vulnerable to damage. Researchers have long wondered how cells can

still make heat shock proteins when all other protein creation is stalled.

Under normal conditions, the cell's protein-building machinery uses a cap, a building block that has been modified through a process called methylation, which recruits the protein-making machinery. But when a cell becomes stressed by heat, this cap becomes inoperative, shutting down the protein-making machinery.

The researchers have discovered that during this shutdown phase, heat shock genes employ an alternate methyl cap, called m6A, to recruit the protein-building apparatus to make heat shock proteins. They made this fundamental discovery while researching a seemingly unrelated "fat- and obesity-associated gene," called FTO, which is "the number one gene linked to obesity," said Qian. People with an allele (genetic variant) of the FTO gene, tend to become obese, and it is also associated with diabetes, he said. The gene produces an FTO enzyme, which acts as a demethylase, or an eraser, of the m6A alternate cap for production of heat shock proteins.

"We found that in a cell lacking FTO [enzymes], the heat shock protein is highly expressed," said Qian. And vice versa, when FTO enzymes are present, heat shock proteins cannot be efficiently made.

In turn, research shows that people with reduced expression of the FTO enzyme "are less likely to be obese," Qian said.

Many years ago, researchers observed that obese people have poor cellular stress responses. This may be because their heat shock proteins are reduced, thereby lowering the cells' protection from other proteins that become damaged and accumulate during stress. "The accumulation of damaged proteins disregulates the whole metabolism," said Qian. "We suspect this could be one cause of obesity." Using animal models, "we are actively working on whether FTO enzymes and their effect on heat

shock genes and proteins could be promoting obesity" and diabetes, he added.

More information: Jun Zhou et al. Dynamic m6A mRNA methylation directs translational control of heat shock response, *Nature* (2015). DOI: 10.1038/nature15377

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