Latest epidemic? High cholesterol, obesity in fruit flies

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Fruit Fly. Credit: UCSD

How do fruit flies get high cholesterol and become obese? The same way as people do - by eating a diet that's too rich in fats.

More importantly, according to two new studies led by a University of Utah human geneticist, fruit flies use the same molecular mechanisms as humans to help maintain proper balances of cholesterol and a key form of stored fat that contributes to obesity. The findings mean that as researchers try to learn more about the genetic and biological processes through which people regulate cholesterol and fat metabolism, the humble fruit fly, also called Drosophila, can teach humans much about themselves.

"Not a lot is known about these regulatory mechanisms in people," says Carl S. Thummel, Ph.D., professor of human genetics at the U of U School of Medicine and senior author on the two studies. "But we can learn a lot by studying metabolic control in fruit flies and apply what we learn to humans."

High cholesterol and obesity, which affects an estimated 25 percent to 30 percent of the U.S. population, are linked to heart disease, diabetes, and other diseases that take huge tolls on health and add billions of dollars to the nation's medical bills. Understanding the processes that regulate cholesterol and fat in humans could be critical for addressing those health risks in people, Thummel believes.

The two studies identify a nuclear receptor, DHR96, which plays a critical role in regulating the balance or homeostasis of cholesterol and another fat molecule called triacylglycerol (TAG). Nuclear receptors are proteins that sense the presence of chemical compounds within cells. DHR96 corresponds closely to a nuclear receptor in humans, called LXR, that is known to regulate cholesterol levels.

In a study published Dec. 2 in *Genes & Development*, Thummel and colleagues at the U of U and two Canadian universities show that DHR96 helps regulate cholesterol in fruit flies by binding with this compound. When this binding occurs, it allows DNA to be read, which switches genes on and off that help maintain proper levels of cholesterol, according to Thummel, who also holds an H.A. and Edna Benning Presidential Endowed Chair in Human Genetics.

The researchers used a technique developed by University of Utah biologist Kent Golic, Ph.D., in which they silenced or disabled the DHR96 protein so it couldn't function in fruit flies. They then grew flies in which DHR96 was silenced. Depending on what the fruit flies were fed, lean or fat diets, they had either too little or too much cholesterol.

Flies fed too little cholesterol died, while those with too much developed hypercholesterolemia or chronically excessive cholesterol levels. At the same time, flies in which DHR96 functioned normally maintained a proper level of cholesterol.

"When they lacked the DHR96 receptor, the flies were unable to maintain cholesterol homeostasis," Thummel says. "This is similar to what happens in humans who have high cholesterol levels."

Fruit flies are good for such research insights in large part because of the insects' short life span - about 30 days - meaning their development and biological processes are more easily observed than in other, longer-lived models, such as mice. Fruit flies also are easy to manipulate genetically and are less expensive to study compared to mice or other models, according to Thummel. In addition, the mechanisms by which metabolism is controlled in fruit flies are very similar to those in mice or humans.

"We can do a lot more mechanistic studies in a fly than are possible in a mouse," he says. "We can study metabolic pathways faster and more in-depth."

Along with its important role in helping to maintain proper levels of cholesterol, DHR96 also plays an integral part in regulating dietary fat metabolism, Thummel and another U of U researcher report in a Dec. 2 study in *Cell Metabolism*.

In flies in which DHR96 was silenced, TAG levels were markedly reduced in the intestine, making the insects resistant to diet-induced obesity. But when DHR96 was overexpressed, meaning there were higher levels of the protein, it led to increased TAG levels and made the flies more prone to being overweight. These findings show that DHR96 is required for breaking down dietary fat in the intestine of fruit flies

and provide insight into how dietary fat metabolism is regulated in Drosophila.

"This nuclear receptor plays a major role in sensing and regulating cholesterol and TAG uptake in the intestine in fruit flies," Thummel says. "It functions similarly to the way LXR functions in humans, although we have a relatively poor understanding about how LXR controls these pathways."

In his future studies, Thummel intends to learn more about how DHR96 regulates metabolism by studying the functions of the genes that it controls.

Source: University of Utah (news : web)