MedicalXpress

A different path to fat-related heart disease

January 18 2011

Heart disease is the leading cause of death for both men and women in the United States. But heart disease is more than just one disease; there are many different 'flavors' that can result from a heart attack, high blood pressure, diabetes or other causes. In lipotoxic cardiomyopathy, for example, heart function is disrupted by fat accumulation in heart cells. Obesity and high-fat diets are major risk factors for lipotoxic cardiomyopathy. A team led by Rolf Bodmer, Ph.D. at Sanford-Burnham Medical Research Institute (Sanford-Burnham) recently unraveled an alternative pathway to lipotoxic cardiomyopathy in fruit flies – a genetic mechanism that occurs independently of a diet high in fat. Their study, published in the January 15 issue of *Genes & Development*, lays the foundation for the development of new ways to combat lipotoxic cardiomyopathy and other types of heart disease.

"It's a well-accepted notion that if you eat too much fatty food and your body can't metabolize it properly, you can become obese and this can lead to lipotoxic cardiomyopathy. Our study shows that there is also an alternative cause of obesity and associated heart problems – an imbalance in the fats that normally make up the basic structure of our cells," explained Hui-Ying Lim, Ph.D., post-doctoral researcher and lead author of the study.

In this study, the researchers analyzed mutant fruit flies (called easily shocked mutants) that have abnormally low levels of phosphatidylethanolamine (PE), a type of fat that makes up a major component of cellular membranes in both flies and mammals. They found that these flies compensate for low PE levels by initiating a

mechanism for synthesizing fat. In this mechanism, a protein called sterol regulatory element-binding protein (SREBP) turns on genes encoding metabolic enzymes that synthesize more fat.

As a consequence of high SREBP, these PE-deficient mutant flies also had high levels of triglycerides, heart-damaging fats commonly associated with obesity and type 2 diabetes in humans. The disruption in cell membrane fat synthesis and consequent triglyceride fat accumulation added up to heart problems for flies short on PE-producing enzymes. Compared to their genetically normal counterparts, they were especially prone to cardiac arrest under stress and other heart problems.

Since overactive SREBP seems to be the cause of heart disease in this system, can it be targeted to reduce heart disease? The researchers addressed this question by inhibiting SREBP or its fat-synthesizing target genes through genetic manipulation. In doing so, they were able to restore fat balance and rescue PE-deficient flies from heart malfunction. These beneficial effects were also achieved by reducing SREBP in just the heart, rather than the whole fly. As a result, the flies were still obese, but their hearts functioned normally. These findings further underscore the importance of SREBP in excess fat-related heart diseases, like lipotoxic cardiomyopathy.

"Here we identified a new metabolic pathway that exhibits striking similarities to obesity- and diabetes-related heart failure in humans," explained Dr. Bodmer, professor and director of the development and aging program at Sanford-Burnham and senior author of the study. "This information might now allow us to interfere with the toxic effects of high fat in the heart by directly manipulating these genes in the heart muscle."

More information: Lim H-Y, Wang W, Wessells RJ, Ocorr K,

Bodmer R. Phospholipid homeostasis regulates lipid metabolism and cardiac function through SREBP signaling in Drosophila. *Genes & Development*. January 15, 2011.