Fruit fly research reveals genetic mechanisms of dietary sugar sensing

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Scientists at the University of Helsinki have identified a sugar sensing regulatory network, which is composed of several genes. Deregulation of this sugar sensing network leads to severely disturbed energy metabolism. The new insight gained in this study may also benefit research into human metabolic diseases such as diabetes.

Changes in nutrient intake require adjustments of the energy metabolism in animals. Therefore, animals have mechanisms to monitor their own nutrient status, collectively referred to as nutrient sensing pathways. The nutrient sensing pathways react to changes in the levels of e.g. sugars, lipids and amino acids and control the metabolism in order to maintain homeostasis.

Sugar feeding activates hormonal mechanisms, such as the secretion of insulin from the pancreas, but sugar levels are also monitored by the so called intracellular sugar sensors. One of such sugar sensors is called Mondo-Mlx. Mondo-Mlx is a transcription factor that controls the activity of other genes.

As a result of research on the fruit fly Drosophila melanogaster, the research group headed by Ville Hietakangas has now discovered that the Mondo-Mlx sugar sensor acts as a master regulator of a large sugar-responsive regulatory network.

"The Mondo-Mlx sugar sensor regulates the majority of sugar responsive genes in several tissues. In addition to the control of metabolic genes, the

Mondo-Mlx sugar sensor also controls other regulatory genes, including other transcription factors such as Sugarbabe, as well as hormones involved in metabolic regulation," says Ville Hietakangas.

The results will also throw new light onto research into human metabolic diseases. Collaboration with the research group of Dr. Samuli Ripatti revealed that many of the Mondo-Mlx target genes were associated with blood triglyceride levels in humans. Elevated blood triglyceride levels are known to increase the risk of cardiovascular diseases.

The Hietakangas group has done basic research on metabolic regulation using the Drosophila model system for several years.

"The Drosophila larvae is an excellent model for studying genetic mechanisms related to nutrient sensing due to the fact that they are constantly eating and the metabolic genes of Drosophila are very similar to those of humans. In addition, the Drosophila genes are easy to manipulate," says Essi Havula, the first co-author of the study.

In previous research the Hietakangas group has already shown that loss of the Mondo-Mlx function leads to severe sugar intolerance.

"Larvae lacking the mlx -gene die as larvae if they are fed food containing sugar. Similar sugar intolerance has been observed in mutant mice. This suggests that the Mondo-Mlx function has been well conserved during evolution, which is a strong indication about the importance of its function," says Ville Hietakangas.

More information: "Mondo-Mlx Mediates Organismal Sugar Sensing through the Gli-Similar Transcription Factor Sugarbabe." *Cell Reports*, DOI: dx.doi.org/10.1016/j.celrep.2015.08.081