Fruit flies and milk sugar

Galactosemia is an inherited metabolic disorder that occurs in roughly 1 of 60,000 babies. It is caused by enzymatic defects in the pathway that processes galactose, a sugar common in dairy products. Affected babies seem healthy at birth but quickly develop acute symptoms when exposed to milk and often die unless the condition is diagnosed. With early detection and strict avoidance of galactose, however, affected babies can survive the neonatal period. Unfortunately, many of them experience severe long-term complications, including organ damage or failure and neurological disabilities. The mechanisms underlying galactosemia are poorly understood; there is no cure, and appropriate treatment is poorly defined. This lack of understanding is partly attributed to the lack of an animal model that accurately mirrors the symptoms and development of galactosemia in humans.

A decade ago, a group of researchers attempted to create a mouse model of galactosemia by deactivating the galactose-processing enzyme (galactose-1-phosphate uridylyltransferase, GALT) that is defective

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in affected humans, but the mice did not develop any symptoms of the disease.

Now, Judith Fridovich-Keil and colleagues (Emory University, Atlanta, GA) have created the first animal model of GALT-deficient galactosemia in the fruit fly (*Drosophila melanogaster*). They first verified that the genes encoding galactose-processing enzymes were similar in flies and humans and then deactivated the gene encoding GALT in flies (*Dis. Models Mech.* doi:10.1242/dmm.005041; published online 2 June 2010). The GALT-deficient larvae died if they were fed galactose but survived if they were fed only glucose, like humans with galactosemia and unlike GALT-deficient mice. Galactose-induced lethality was dose-dependent and sugar-specific. Restricting galactose in the flies' diet allowed them to survive, but they still experienced neurological or neuromuscular deficits, like humans with galactosemia. Notably, sensitivity to galactose in the larvae was also time-dependent; GALT-deficient larvae died within days if they were transitioned from a glucose-only diet to a glucose–galactose diet, whereas adult GALT-deficient flies did not.

Next, the scientists engineered the GALT-deficient flies to express a human *GALT* transgene. Expression of the transgene prevented galactose-induced lethality and neurological symptoms in GALT-deficient flies.

These results confirm that GALT-deficient fruit flies recapitulate both acute and long-term symptoms of galactosemia in humans. Establishment of this model opens the door for studies to explore the factors that contribute to development of this disease as well as its ongoing pathophysiology. Fridovich-Keil and her group have already started to investigate the timing, extent and causes of sensitivity to galactose in this fly model.

Monica Harrington

EXPLAINING A RARE DISORDER

In an effort to better understand the molecular basis of a complex inherited disorder, a group of researchers has developed a way to simultaneously study the effects of multiple mutations associated with the disorder (*Proc. Natl. Acad. Sci. USA* published online 24 May 2010; doi:10.1073/pnas.1000219107). The team, led by Nicholas Katsanis of Duke University (Durham, NC), used zebrafish to analyze the functions of the 125 mutations known to be associated with Bardet-Biedl syndrome (BBS).

BBS is a ciliopathy, meaning that people who have BBS have defective cilia, finger-like projections that stick out of many types of cells. People with BBS can have a variety of symptoms, including damaged retinas, obesity, mental retardation and more than the usual number of toes or fingers. These traits vary greatly between people who have BBS, hinting at the syndrome's complex genetic underpinnings.

Katsanis and his team first carried out *in vivo* tests in zebrafish embryos to determine whether specific mutations would cause the zebrafish to develop specific defects. They then carried out *in vitro* tests on cells to find out if any of the unusual zebrafish embryo activity that they had observed in the *in vivo* tests could be explained by defective mammalian cell behavior. They found that mutations in 1 of 14 genes known to be associated with BBS are responsible for the disorder. Further analysis showed that common mutations in other genes, which researchers previously thought were benign, may modify the severity and diversity of the symptoms of BBS.

To determine the sensitivity and accuracy of their *in vivo* results, the researchers compared their data with results from previous clinical studies. They found that their tools predicted that 48 of 49 alleles previously known to be pathogenic were indeed pathogenic, suggesting their method had a sensitivity of 98%. Out of 17 mutations known to be benign, 14 showed up as benign in all of the *in vivo* assays, suggesting a false-positive rate of less than 10%.

According to Katsanis, their study shows that it is possible to use a vertebrate model to predict whether a specific mutation plays a role in a complex disease. "A next step is to develop similar tools to let us evaluate various human genetic mutations within the context of their functions," Katsanis said in a press release. "Genotype must have a predictive value or it doesn't tell us much. Knowing all of the disease-related variants in a genome is only a starting point."

Kirsten Dorans