Life without TORC is 1 big struggle

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Humans and fruitflies – those pesky little buggers that are irresistibly attracted to overripe fruit – share more than a sweet tooth. Both rely on the same insulin-regulated molecular pathway to maintain their energy balance when starved for food, reports a team of researchers at the Salk Institute for Biological Studies.

Their findings, published in the May 7, 2008 issue of *Cell Metabolism*, shows that the same genetic switch that revs up glucose production in human livers during lean times serves as a key biochemical control point linking feeding, energy stores and stress resistance in the Drosophila. Without out it, the flies' lives are cut short by stress and starvation.

"Basic biological processes are remarkably well conserved through evolution. Although flies are less complicated than mammals, fasting triggers similar changes in behavior, physical activity, and metabolism," explains Marc Montminy, Ph.D., a professor in the Clayton Foundation Laboratories for Peptide Biology, who teamed up with fly expert John Thomas, Ph.D., a professor in the Molecular Neurobiology Laboratory for the current study.

But it's not simply a case of "more of the same." "You may wonder why do these experiments in flies"" asks Thomas. "The major reason is that we can capitalize on the genetics of flies to really understand TORCs function and then carry that information back into mouse models."

Small and easy to breed, Drosophila melanogaster is probably the most studied organism in biological research. And although they lack a

pancreas, they have specialized cells in their brains that produce hormones similar to insulin and glucagon that mimic the function of their human counterparts.

After a meal, the cells release insulin into the circulatory system, which signals the “fat body,” the flies’ energy-storing organ, to squirrel away fat and sugar. When the amount of sugar drops during prolonged periods of fasting, adipokinetic hormone, the fly homolog of glucagon, instructs the body to dip into the fat body’s stock of lipids and glucagon. Not surprisingly, animals with a well-filled pantry are more resistant to starvation.

In earlier mouse studies, Montminy discovered a metabolic switch, a protein called TORC2, which turns on gluconeogenesis in the liver when blood glucose levels run low.

To understand TORCs role in fly metabolism, a team of researchers who split their team between Montminy’s and Thomas’ lab, first established that in well-fed flies, just like in non-fasting mice, the protein is marooned outside the cell’s nucleus. When tough times hit, either because the researchers withheld food or mixed in paraquat, a substance that produces oxidative stress, TORC slipped into the nucleus and activated a network of genes to remedy the stressful situation.

Without functional TORC, the flies’ life expectancy was cut in half when subjected to the same kind of stressors. The TORC mutant flies were also unable to store energy in their fat body. Restoring TORC expression in the nervous system rescued the flies’ starvation and stress resistance, although their glycogen and lipid stores were not fully replenished.

“This finding told us that TORC may do more in the brain than maintain

energy balance," explains postdoctoral researchers and first author Biao Wang, Ph.D. "We can now use TORC as a starting point to understand the underlying mechanisms of diabetes by carrying out genetic screen. That is the beauty of the fly system."

After it had become clear that fasting put TORC to work in the nucleus, the researchers wondered whether refeeding recalled the activated genetic switch. In response to rising insulin levels the enzyme SIK2 tagged TORC and sent it to the cellular recycling bin. Without SIK2 to take TORC out of commission, the flies were super-resistant to starvation and stress and lived 50 percent longer without food than their normal counterparts.

"Beyond its role in glucose and fat metabolism, insulin also regulates longevity in Drosophila and other organisms," explains Montminy." Based on insulin's ability to shut down the TORC switch during feeding, we can now examine whether TORC has some effect on lifespan."

Source: Salk Institute