Super-size flies

The increasing prevalence of obesity and other nutrition-related chronic diseases has prompted considerable efforts to understand their pathogenesis and treatment. One experimental approach is to overexpress, inactivate, or manipulate specific genes that regulate energy metabolism and fat storage. Many such techniques are fully established, routine tools in *Drosophila* and *C. elegans*, which provide elegant models for dissecting endocrine problems and metabolic pathways.

In the past decade, obesity has been recognized as an increasing threat to global health, with numerous associated life-threatening complications, including diabetes, heart disease, hypertension, and cancer (Flegal et al., 2002; Kopelman, 2000). To maintain constant weight, energy intake (food eaten) must equal energy consumed (by metabolism). Any imbalance is reflected in a change in the amount of stored energy, mainly as fat (Figure 1). Fat in the form of triacylglycerols (TAG) is found in intracellular neutral lipid droplets that occupy the major volume of adipocytes but are also present in virtually all cell types. Regulation of fat depots involves a complex interplay between central regulators of feeding behavior in the nervous system, neuroendocrine signals, and metabolic regulators of energy expenditure and fat storage (Flier, 2004). Genetic analysis has the potential to identify new players in these processes, each of which in turn represents a potential target for prevention or treatment of obesity and its medical consequences. In this issue of *Cell Metabolism*, Grönke and colleagues employ a genetic strategy to identify such a candidate from the fruit fly *Drosophila*: *brummer*, which encodes a triacylglycerol lipase (Grönke et al., 2005; [this issue of Cell Metabolism]).

Our current understanding of the molecular mechanisms underlying fat storage and utilization derives largely from studies in cultured mammalian adipocytes. Studies of transgenic and knockout mice have also advanced our understanding of the regulation of food consumption, body composition, and metabolic rate (Friedman, 2003; Flier, 2004; O'Rahilly et al., 2003). Although genetics has been applied successfully in mammalian model systems, only a small fraction of the genes influencing obesity have so far been identified (Barsh and Schwartz, 2002). Among the most consequential discoveries were the *ob* gene product Leptin (Zhang et al., 1994) and its receptor (Tartaglia et al., 1995).

Recently, nonmammalian genetic model organisms including nematodes (*Caenorhabditis elegans*) and fruit flies (*Drosophila melanogaster*) have emerged as excellent paradigms for research on the physiology of obesity. A genome-scale RNAi screen in nematodes identified more than 400 genes whose inactivation results in either increased or decreased fat (Ashrafi et al., 2003). The identified genes included those involved in fat and cholesterol metabolism; about 100 have mammalian orthologs that are known to function in lipid homeostasis. New candidate genes were also identified, including some that function in the central nervous system. More than half of the identified genes have mammalian orthologs not previously implicated in fat deposition. This study underscores the value of genetic analyses of nonmammalian model organisms in elucidating the physiological basis of mammalian obesity.

Drosophila is emerging as another powerful system to study obesity. In flies, the masses and sheets of adipose tissue that are distributed throughout the organism are collectively called the fat body. Like mammalian adipocytes, insect fat body cells constitute the animal's major energy reserve, accumulating TAG in intracellular lipid droplets. This conserved function suggests that the underlying machinery and control mechanisms of fat storage are also evolutionarily conserved. A regulated balance between lipogenesis and lipolysis (TAG mobilization) maintains organismal fat storage to a genetically determined set point.

In this issue of *Cell Metabolism*, Grönke and colleagues describe their genome-wide transcriptome analysis of fed and food-deprived adult flies to identify nutritionally regulated genes. The 223 differentially regulated genes include genes involved in carbohydrate, amino acid, and lipid catabolism, as well as 25% with no assigned function. One gene upregulated upon starvation is *brummer (bmm)*, a homolog of human triacylglycerol lipase (ATGL). *bmm* is highly enriched in fat body cells, as well as in the larval midgut and gastric caeca. Interestingly, its expression in response to food deprivation and refeeding post-starvation implicate *brummer* in the regulation of energy metabolism. Phylogenetic analysis indicates that Bmm is an evolutionarily conserved triacylglycerol lipase, with a conserved region that contains a patatin-like domain (PLD) including a serine hydrolase motif and a Brummer box. Grönke and coworkers further demonstrate that recombinant Bmm can cleave TAG in vitro, whereas an enzymatically inactive catalytic mutant has no activity.

To test whether *bmm* promotes fat mobilization in vivo, the authors generated *bmm* loss-of-function mutants. Interestingly, while embryos lacking both maternal and zygotic *bmm* activity die, flies lacking only zygotic Bmm lipase activity develop normally but show progressive development of obesity as measured by an increased amount of organismal TAG relative to protein content, as well as an increased size and number of lipid storage droplets in single fat body cells. Conversely, overexpression of *bmm* in fat body cells of fed flies, which recapitulates the starvation-induced upregulation of *bmm* transcription, depletes TAG content significantly. The latter effects were not observed upon expression of an enzymatically inactive *bmm* transgene. Excessive fat storage in flies lacking *bmm* function reduces the median life span by only 10%, and acute TAG mobilization is impaired but not completely abolished in *bmm* mutants. Taken together, these results suggest that, like in mammals, mobilization of TAG storage in flies is controlled by more than one TAG lipase.

To further demonstrate the functional

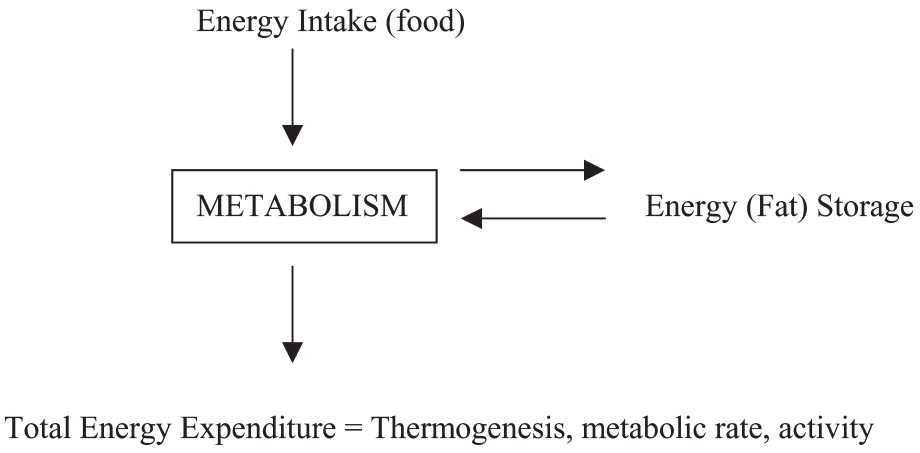

Figure 1. Fat stores represent the net balance between energy intake and energy expenditure

similarity between mammalian and *Drosophila* TAG lipases, the authors showed that EGFP-tagged Bmm localizes at the surface of lipid droplets. Finally, the authors show that Bmm and the fly Perilipin-like gene *LSD-2* act antagonistically to regulate fat storage in vivo. This finding is entirely consistent with what is known in the mammalian system, where Perilipin has been shown to coat adipocyte lipid droplets and is postulated to modulate the hydrolysis of triacylglycerols. Perilipin-deficient mice are lean with constitutive activation of adipocyte lipolysis and resist high-fat diet-induced obesity (Tansey et al., 2001).

The identification and characterization of Bmm demonstrates the conservation of effectors controlling organismal fat storage in mammals and flies and emphasizes the value of *Drosophila* for research in energy homeostasis. Although much evidence suggests that abnormalities in energy expenditure and regulation of fat storage contribute to the development of obesity, the molecular mechanisms that control these processes in humans are not well understood. Identifying the genetic causes of decreased energy expenditure and chronic imbalance of energy storage and developing therapies designed to specifically target the same in obese humans have proved difficult. Work that integrates knowledge from the genome project, along with studies in which candidate genes can be identified and manipulated and effects on whole-body energy homeostasis evaluated (Grönke et al., 2005), is required in order to identify the molecular mechanisms responsible for regulating energy balance.

Clearly, model organisms like *C. elegans* and *Drosophila* offer exciting prospects for obesity research. Because of their short generation time and ease of breeding very large numbers of individuals, and the existence of powerful tools for genetic mapping and high-throughput methods for creation of mutants and phenocopies, identification of genes influencing specific phenotypes can be accomplished much more rapidly than in mice or humans. These experimental advantages are ideal for performing second site modifier screens and should aid greatly in the analysis of complex multigenic disorders. Validation of the mouse and human homologs of the genes identified from worm and fly studies will be an excellent strategy to accelerate the identification of molecular targets that may eventually produce safe and effective therapies for obesity and its related disorders.

DOI 10.1016/j.cmet.2005.04.008

Meghana M. Kulkarni
and Norbert Perrimon
Department of Genetics
Howard Hughes Medical Institute
Harvard Medical School
77 Avenue Louis Pasteur
Boston, Massachusetts 02115

Selected reading

Ashrafi, K., Chang, F.Y., Watts, J.L., Fraser, A.G., Kamath, R.S., Ahringer, J., and Ruvkun, G. (2003). Nature *421*, 268–272.

Barsh, G.S., and Schwartz, M.W. (2002). Nat. Rev. Genet. *3*, 589–599.

Flegal, K.M., Carroll, M.D., Ogden, C.L., and Johnson, C.L. (2002). JAMA *288*, 1723–1727.

Flier, J.S. (2004). Cell *116*, 337–350.

Friedman, J.M. (2003). Science *299*, 856–858.

Grönke, S., Mildner, A., Fellert, S., Tennagels, N., Petry, S., Müller, G., Jäckle, H., and Kühnlein, R.P. (2005). Cell Metabolism *1*, this issue, ■■■–■■■.

Kopelman, P.G. (2000). Nature *404*, 635–643.

O'Rahilly, S., Farooqi, I.S., Yeo, G., and Challis, B.G. (2003). Endocrinology *144*, 3757–3764.

Tansey, J.T., Sztalryd, C., Gruia-Gray, J., Roush, D.L., Zee, J.V., Gavrilova, O., Reitman, M.L., Deng, C.X., Li, C., Kimmel, A.R., and Londos, C. (2001). Proc. Natl. Acad. Sci. USA *98*, 6494–6499.

Tartaglia, L.A., Dembski, M., Weng, X., Deng, N., Culpepper, J., Devos, R., Richards, G.J., Campfield, L.A., Clark, F.T., Deeds, J., et al. (1995). Cell *83*, 1263–1271.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., and Friedman, J.M. (1994). Nature *372*, 425–432.