Cell Metabolism
Previews

Putting the Brakes on Dietary Fat Breakdown

Ronald P. Kühnlein[1,*]
[1]Department of Molecular Developmental Biology, Max-Planck-Institut für biophysikalische Chemie, 37077 Göttingen, Germany
*Correspondence: rkuehnl@gwdg.de
DOI 10.1016/j.cmet.2009.11.004

Dietary lipid digestion is critical for body fat storage control, but little is known about the regulation of genes involved in fat breakdown and absorption in the gastrointestinal tract. A *Drosophila* study (Sieber and Thummel, 2009 [this issue of *Cell Metabolism*]) now demonstrates that the orphan nuclear receptor DHR96 adjusts fat storage in flies by tuning gastric lipase expression.

"Dosis sola facit venenum," the visionary statement of the Renaissance scholar Paracelsus that it is only the dose which makes a thing poison, likewise applies to fat, the calorically most important energy currency of animals. Although body fat storage is essential for survival, excessive lipid accumulation represents a severe health threat, as witnessed by the increasing number of obesity cases in human populations. Accordingly, organisms employ a complex regulatory network involving numerous organs including the central brain, the adipose tissue, and the digestive tract to properly balance the incessant fluctuations in energy intake and expenditure (Galgani and Ravussin, 2008). Human body fat regulation is admirably flexible but still occasionally overstrained by the unfortunate combination of sedentary lifestyle and high-calorie diets.

For those of us who surrender to the seductive call of fatty fries, the breakdown and absorption in the digestive tract is the first gateway of the dietary lipid's journey from the plate to the love handles (Figure 1). Weight loss drugs such as Orlistat exploit this gateway by inhibiting digestive lipases, a mechanism which blocks dietary fat breakdown and dooms the surplus calories to excretion (Figure 1). Given the proven effectiveness of restricting fat digestion as a means of body fat control, surprisingly little is known about the transcriptional regulation of factors that metabolize dietary lipids in the digestive tract. A new study by Sieber and Thummel (Sieber and Thummel, 2009) now demonstrates an unexpected central role of a nuclear receptor in body fat control operating in the digestive system of flies.

The nuclear receptor superfamily consists of a large number of ligand-regulated transcription factors controlling a plethora of metabolic functions. Members of the xenobiotic subfamily of nuclear receptors represented by the mammalian pregnane X receptor and the constitutive androstane receptor play important roles in sensing and detoxification of xenochemicals. More recent evidence, however, also indicates that these nuclear receptors are involved in hepatic lipometabolism control (Moreau et al., 2008). Much like its mammalian relatives, the single *Drosophila* member of the xenobiotic nuclear receptor subfamily called DHR96 has been initially implicated in protecting the fly against xenochemicals (King-Jones et al., 2006). A careful reanalysis of DHR96 mutants revealed now new talents of this transcription factor.

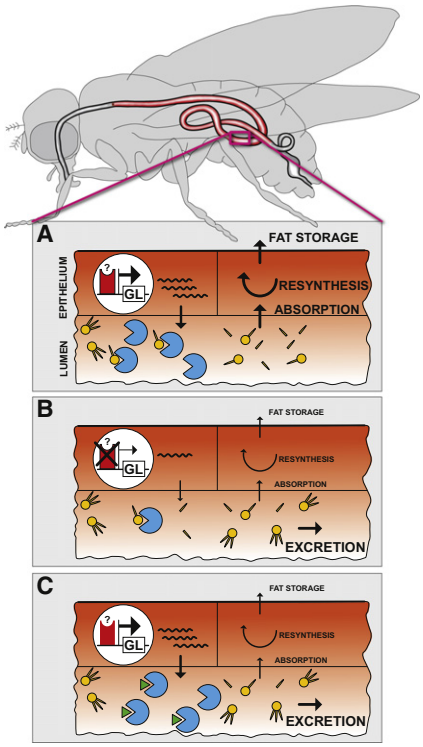

Figure 1. Nuclear Receptor DHR96 Regulates Gastric Lipase to Control Fat Storage in Flies
(A) In the fly midgut epithelium, DHR96 (red; modulated by an unknown ligand [?]) controls gastric lipase (GL) transcription. Lumenal gastric lipase enzyme (blue) breaks down dietary fats (yellow) destined for absorption/resynthesis in the gut epithelium and final storage in the adipose tissue.
(B) Reduction of gastric lipase transcription in DHR96 mutants causes leanness by redirecting the majority of dietary fat to excretion.
(C) Similarly, lipase inhibitors (green) such as Orlistat prevent dietary fat uptake in the digestive tract.

DHR96 mutant flies are lean despite normal food intake, and they show enviable resistance to obesity on a high-calorie diet. The key to the mechanistic understanding of this phenotype came from two observations. First, the leanness of DHR96 mutants is cured when flies are offered a diet supplemented with free fatty acids. Second, DHR96 mutants are unresponsive to Orlistat, suggesting that the breakdown of dietary fat is the limiting factor for body fat accumulation. Indeed, lipase activity in the midgut of DHR96 mutants is dramatically reduced, and the authors identified a gastric lipase as a (likely) direct target of DHR96 transcriptional regulation. Consistently, knockdown of the gastric lipase slims wild-type flies, whereas overexpression of the gene restores normal body fat content of DHR96 mutants. The critical role of fat digestion for adjusting body fat is emphasized by the fact that DHR96 inactivation reverts the adipose phenotype of fly obesity models with impaired storage lipid mobilization (Grönke et al., 2007).

Does DHR96 act as the conductor of a string quartet with gastric lipase as first violin? More likely the nuclear receptor masters a symphonic orchestra with the lipase as concertmaster. Microarray experiments identified numerous gut-expressed genes as DHR96 targets,

among them central regulators of cholesterol metabolism. Accordingly, a more comprehensive appraisal of DHR96 function in lipometabolism has to await continuative, functional studies on its other target genes. As it is the baton which grants the conductors control over the orchestra, it is the ligand which empowers nuclear receptors. As yet DHR96 is an orphan nuclear receptor but belongs to a family in which some members made their career as prominent drug targets. Accordingly, the identification of the endogenous DHR96 ligand(s) is an outstanding future challenge in view of the potential functional conservation among the xenobiotic receptors of flies and man with respect to the presented novel mode of fat storage control.

Showing that Orlistat slims *Drosophila* is not only good news for flies concerned about their "wasp waists." This finding also provides proof of concept for small compound in vivo screens to identify modulators of dietary fat digestion using the fly model. Collectively, this study underscores the value of *Drosophila* as a rising model system for energy metabolism research (Baker and Thummel, 2007; Schlegel and Stainier, 2007) with relevance for the understanding of physiological and pathophysiological processes in fat storage regulation of mammals and man.

REFERENCES

Baker, K., and Thummel, C.S. (2007). Cell Metab. *6*, 257–266.

Galgani, J., and Ravussin, E. (2008). Int. J. Obes. *32*, S109–S119.

Grönke, S., Müller, G., Hirsch, J., Fellert, S., Andreou, A., Haase, T., Jäckle, H., and Kühnlein, R.P. (2007). PLoS Biol. *5*, e137. 10.1371/journal.pbio.0050137.

King-Jones, K., Horner, M.A., Lam, G., and Thummel, C.S. (2006). Cell Metab. *4*, 37–48.

Moreau, A., Vilarem, M.J., Maurel, P., and Pascussi, J.M. (2008). Mol. Pharm. *5*, 35–41.

Schlegel, A., and Stainier, D.Y. (2007). PLoS Genet. *3*, e199. 10.1371/journal.pgen.0030199.

Sieber, M.H., and Thummel, C.S. (2009). Cell Metab. *10*, this issue, 481–490.

How Iron Controls Iron

Lukas C. Kühn[1,*]
[1]Ecole Polytechnique Fédérale de Lausanne (EPFL), ISREC - Swiss Institute for Experimental Cancer Research, 1015 Lausanne, Switzerland
*Correspondence: lukas.kuehn@epfl.ch
DOI 10.1016/j.cmet.2009.11.005

Cells regulate iron homeostasis by posttranscriptional regulation of proteins responsible for iron uptake and storage. This requires RNA-binding activity of iron-regulatory proteins, IRP1 and IRP2. Two studies recently published in *Science* by Vashisht et al. (2009) and Salahudeen et al. (2009) reveal how cells adjust IRP2 activity.

Iron-containing enzymes are essential for the survival of both uni- and multicellular organisms, as they function in energy-producing redox reactions, oxygen transport, DNA synthesis, and cellular detoxification. Iron associates with proteins most commonly by its insertion into a porphyrin ring as heme or its assembly with sulfur in Fe-S clusters. In some proteins, di- or trivalent iron is bound directly to specific pockets in the secondary structure. Prior to its incorporation, iron needs to be bioavailable as "free" iron. This free iron is potentially harmful because of its ability to generate reactive oxygen species through Fenton chemistry. Thus, cells must carefully regulate iron homeostasis to ensure sufficient iron supply while limiting iron toxicity.

In mammals, two distinct regulatory circuits control body and cellular iron homeostasis. Body iron is sensed by the liver, which in response to high iron synthesizes and secretes hepcidin. This peptide hormone negatively regulates iron export from intestinal cells to limit iron absorption from the diet. Cellular iron homeostasis is achieved by the cytoplasmic RNA-binding proteins IRP1 and IRP2, which regulate posttranscriptionally the fate of mRNAs encoding proteins crucial for iron metabolism, such as transferrin receptor 1 (TfR1) and ferritin H and L (Figure 1). At low cellular iron concentrations, IRPs are active and bind to conserved RNA hairpin structures, known as iron-responsive elements (IREs). Binding to five IREs in the 3′ untranslated region of TfR1 mRNA inhibits mRNA degradation, thereby increasing TfR1 expression and iron uptake. Binding to one IRE in the 5′ untranslated region of ferritin mRNA inhibits ferritin translation, thereby reducing cellular iron storage. Increased iron uptake and reduced iron storage cumulatively augment the free iron pool. High iron levels, in turn, inactivate IRP1 and IRP2 RNA-binding activity. IRP1 inserts a 4Fe-4S cluster, which converts it into a cytosolic aconitase, while IRP2 is targeted for proteasomal degradation. Initial studies concluded that a unique 73 amino acid region of IRP2, which is absent in IRP1, was modified by iron-dependent oxidation and then recognized by heme-oxidized IRP2 ubiquitin ligase 1 (HOIL-1) (Yamanaka et al., 2003). These conclusions were, however, contradicted by studies showing that deletion of the 73 amino acid region or RNA interference against HOIL-1 did not abrogate iron-dependent IRP2 degradation (Hanson et al., 2003; Wang et al., 2004; Zumbrennen et al., 2008). In addition, a constitutive apo-IRP1 mutant was sensitive to iron-dependent proteasomal degradation,