You are what you secrete

Obesity and insulin resistance enjoy a complex relationship that gives rise to a range of metabolic disorders, including type 2 diabetes, dyslipidemia and coagulation disorders. Teasing apart this relationship could yield new therapies to treat some of these conditions and two new reports point to the adipocyte-secreted protein, adiponectin, as a new molecular target. (pages 941–946 and pages 947–953)

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Our notion of the adipocyte as merely a cargo space for fat has undergone a dramatic change[1]. These unexciting cells were once considered to be inert depots for storing fuel as lipid, to be released only during times of hardship such as fasting or starvation. Since an excess of adipose tissue is associated with dyslipidemia, obesity and the insulin resistance of type 2 diabetes, it was accepted wisdom that overloading the capacity for fat storage, combined with excessive lipolysis and release of free-fatty acid, caused defects in glucose homeostasis as a consequence of fuel partitioning. However, the severe loss of fat tissue, as characterized by lipodystrophy, also leads to numerous metabolic abnormalities such as insulin resistance and diabetes[2].

We now know that adipose tissue is much more complex than previously thought, and that it operates as an endocrine organ that releases hormones in response to specific extracellular stimuli or changes in metabolic status. These secreted proteins, which include tumor necrosis factor (TNF)-α, leptin, adipsin, resistin and adiponectin (also known as Acrp30 or adipoQ), perform diverse functions, but seem to share some structural properties of cytokines. They have therefore been referred to collectively as 'adipokines'. Although they seem to play important regulatory roles in a variety of complex processes, including fat metabolism, feeding behavior, hemostasis, vascular tone, energy balance and insulin sensitivity, none is without controversy regarding its respective mechanism and scope of action. Moreover, dynamic interactions between these proteins are likely to influence their activities, and dictate the extent to which insulin is sensed in its target tissues. Thus, the activities of adipokines might hold the key to understanding the fine-tuning of metabolism, and the development of hypertension, central adiposity, disorders of coagulation and glucose intolerance—symptoms commonly associated with the insulin resistance syndrome. Two papers in this issue describe an exciting new property for one of these adipokines, adiponectin[3,4].

Several groups originally identified the gene encoding the complement-related protein, adiponectin, based on its adipocyte-specific expression and secretion[5,6]. Its globular domain, critical for bioactivity, is conserved in proteins with structural similarity to TNF-α (ref. 7). Interestingly, the expression of adiponectin mRNA and protein are reduced in obese mice and humans[8], indicating that it might function as an adipostat in regulating energy balance and that its deficiency might contribute to the obesity-dependent development of diabetes. Yamauchi *et al.*[4] confirm this observation in two models of insulin resistance by demonstrating reductions in mRNA and circulating levels of adiponectin during high-fat feeding of mice, as well as in lipoatrophic peroxisome proliferator-activated receptor (PPAR)-$\gamma^{+/-}$ mice treated with a retinoid-X receptor (RXR) antagonist. Conversely, Berg *et al.*[3] observe that caloric restriction increases the levels of the protein. Both groups show that treatment of insulin resistant mice with insulin sensitizing PPAR-γ activators such as rosiglitazone increases adiponectin levels. Thus, adiponectin expression correlates well with the insulin sensitive state, and its absence is associated with insulin resistance and dyslipidemia. Moreover, adiponectin might mediate some of the insulin-sensitizing effects of PPAR-γ modulators.

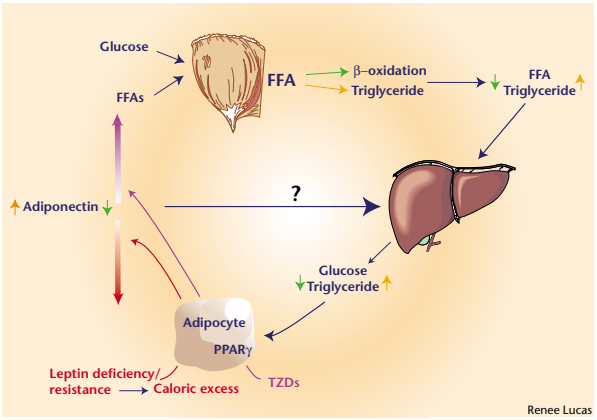

Fig. 1 A hypothetical model for the secretion and action of adiponectin. The synthesis and secretion of adiponectin is increased by activation of the nuclear receptor PPAR-γ, and reduced by caloric excess, presumably associated with leptin deficiency or resistance. Once released, adiponectin can directly increase fatty-acid transport, oxidation and dissipation in skeletal muscle, reducing the levels of intramyocellular lipids, thus improving insulin signaling. The protein can also increase the sensitivity of the hepatocyte to insulin, either through a direct action, or indirectly by lowering circulating lipids due to its action on muscle. Thus, administration of adiponectin can result in improved insulin sensitivity and glucose tolerance, and can correct hyperglycemia associated with obesity.

To determine whether these correlative findings are meaningful, both groups administered purified adiponectin directly to normal or diabetic mice. The protein acutely normalizes blood sugar in leptin-deficient *ob/ob* mice, but surprisingly does not correct the hyperinsulinemia in these animals. Berg *et al.* show that the protein is also effective in postprandial normal mice, and in a model of type 1 diabetes, indicating that little if any insulin is required to observe its effect *in vivo*. These data are not generally consistent with the actions of an insulin sensitizer, which would be expected to be ineffective in insulinopenic models, and to lower endogenous insulin in hyperinsulinemic insulin-resistance models[9]. However, injection of adiponectin into diabetic *db/db* or KKAy mice clearly reduced insulin resistance and improved glucose tolerance, correcting both hyperglycemia and hyperinsulinemia[4]. Lipoatrophic mice also responded to adiponectin, although co-administration of leptin was required for full restoration of normal glycemia.

In addition to the uncertainty regarding the insulin-sensitizing effects of adiponectin, its site of action remains controversial. Berg *et al.* suggest that the protein sensitizes the liver to the anti-gluco-

neogenic effects of insulin, but does not produce a sustained attenuation of triglyceride accumulation in this tissue. In contrast, Yamauchi *et al*. speculate that adiponectin works primarily in the muscle to burn fat, similar to observations by Fruebis *et al*. earlier this year[5]. There seems to be a strong correlation between intramuscular triglyceride content and insulin resistance in animal models as well as in patients with type 2 diabetes[2]. Adiponectin might diminish these levels by increasing β-oxidation of fatty acids, in the process reducing serum triglyceride and levels of free-fatty acid, and thus indirectly improving insulin sensitivity of the liver.

How does adiponectin produce this profound change in muscle lipid metabolism? Adiponectin increases expression of the genes encoding CD36, acyl CoA oxidase and uncoupling protein-2 (UCP2), which might enhance fatty-acid transport, fat combustion and dissipation, respectively. This treatment also correlated with improvements in insulin receptor signaling. Given that lipid infusion is known to acutely attenuate the activation of the PI 3-kinase pathway by insulin in skeletal muscle[10], these data indicate that the insulin sensitizing effect of adiponectin is secondary to its ability to burn fat, presumably due to the aforementioned changes in gene expression. No doubt future studies will focus in more detail on the mechanism of action of the protein, the signaling pathways it uses, and the possible interaction with other adipokines that might act in synergy, such as leptin, or in opposition, such as resistin or TNF-α.

Is adiponectin the crucial, long-sought link between obesity and insulin resistance? Although this protein is unlikely to fully explain the relationship, it is hard to resist the speculation that adiponectin or synthetic analogs might be useful in the treatment of type 2 diabetes, and perhaps other states characterized by insulin resistance. A locus was identified in a genome-wide scan for type 2 diabetes that included the adiponectin gene[11]. Moreover, a recent study revealed a single nucleotide polymorphism in a Japanese population with increased risk for type 2 diabetes (Kadowaki *et al*., manuscript submitted). These findings are highly preliminary, but lend credence to the idea that adiponectin or perhaps its putative receptor might represent an exciting target for the development of drugs for diabetes or perhaps even obesity. Either way, an agent that burns fat is certain to be a big hit.

1. Spiegelman, B.M. & Flier, J.S. Obesity and the regulation of energy balance. *Cell* **104**, 531–543 (2001).
2. Saltiel, A.R. New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell* **104**, 517–529 (2001).
3. Berg, A.H., Combs, T.P., Du, X., Brownlee, M. & Scherer, P.E. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nature Med.* **7**, 947–953 (2001).
4. Yamauchi, T. *et al.* The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nature Med.* **7**, 941–946 (2001).
5. Scherer, P.E., Williams, S., Fogliano, M., Baldini, G. & Lodish, H.F. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J. Biol. Chem.* **270**, 26746–26749 (1995).
6. Hu, E., Liang, P. & Spiegelman, B.M. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J. Biol. Chem.* **271**, 10697–10703. (1996).
7. Fruebis, J. *et al.* Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc. Natl. Acad. Sci. USA* **98**, 2005–2010 (2001).
8. Kahn, B.B.& Flier, J.S. Obesity and insulin resistance. *J. Clin. Invest.* **106**, 473–481 (2000).
9. Olefsky, J.M. & Saltiel, A.R. PPARγ and the treatment of insulin resistance. *Trends Endocrinol. Metab.* **11**, 362–368 (2000).
10. Shulman, G.I. Cellular mechanisms of insulin resistance. *J. Clin. Invest.* **106**, 171–176 (2000).
11. Kissebah, A.H. *et al.* Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. *Proc. Natl. Acad. Sci. USA* **97**, 14478–14483 (2000).

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Cystic fibrosis salt/fluid controversy: In the thick of it

A new study shows that a mouse model of cystic fibrosis has lower levels of liquid on the surface of its airway epithelium which suggests that thickened airway secretions might have a role in the disease process and that rehydrating the airways might be of benefit to patients.

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Cystic fibrosis (CF) is associated with impaired mucociliary clearance, abnormal mucous, inflammation and chronic respiratory infections by bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*[1]. Although it is recognized that lung damage caused by bacterial infection is a major component of the disease, it has been difficult to understand why the lungs of CF patients become colonized with bacteria. Normal human airways are continually exposed to bacteria but the lower airways remain sterile in healthy individuals. The normal airway has many lines of defense against bacterial colonization, including protective processes such as mucociliary clearance that traps and removes inhaled bacteria, and cell-surface barriers that limit the ability of bacteria to bind to the airway epithelium. Recently, two competing theories have been proposed to explain how bacterial colonization occurs in CF. One theory, the 'fluid' model, contends that hyper-absorption of fluid by the airway surface epithelium leads to a lower than normal airway-surface liquid (ASL) volume (Fig. 1*a*). This reduced volume, combined with defective fluid production by the submucosal glands, in turn leads to under-hydrated mucous and impaired mucociliary clearance. Impaired mucociliary clearance and thick airway secretions contribute to the establishment of an environment in the airway that promotes colonization of the lungs by bacteria[2]. The second theory, the 'salt' model, states that the salt content of airway fluid in CF is too high and thus prevents salt-sensitive defensin molecules in the ASL from killing bacteria, leading to increased susceptibility to lung infections[3]. The two theories describe two different ways of developing therapeutic strategies. Whereas the fluid model predicts that adding more liquid to the airway surface would improve health, the salt model predicts that reducing the salt concentration of the airway fluid to reactivate the natural defenses against infection would be a better therapeutic strategy. Resolution of the salt-fluid controversy thus has important implications to the design of therapeutic strategies for CF.

An article in the 22 July issue of *Molecular Cell* by Tarran *et al*.[4] adds support to the fluid model. The authors studied the nasal epithelium of the mouse deficient in the gene implicated in CF as a model for the human disease. They found a substantial increase in the number and size of the goblet cells and a profound decrease in ASL volume in the CF mice compared with wild-type mice. Because in the mouse, goblet cells produce mucous, an increase in the size and number of these cells in the CF mouse might indicate that the nasal epithelium of the mouse responds to a reduc-