editorial

The adipocyte comes of age

This past decade has been very good to the adipocyte. For many years, the adipocyte was only recognized for its role as a fat storage cell and, in the case of brown adipose, for thermogenesis. However, adipocyte science now describes a far more complex tissue, an endocrine organ that exerts a profound influence on other tissues and the whole animal. Therefore, we are pleased to bring you a Thematic Review Series on Adipocyte Biology, and several experts in the field were invited to contribute.

Adipose tissue came of age as an endocrine organ with the discovery of leptin in 1994. First identified as a satiety hormone that is mutated in the *obese* mouse, leptin has been shown to also play a role in the regulation of the basal metabolic state. It regulates many aspects of metabolism, in part through its activation of AMP-activated protein kinase. Leptin's functions extend beyond metabolism. For example, leptin is essential for fertility and plays a role in immune function. With leptin as a precedent, other adipose-derived hormones, now known as "adipokines," have been identified, including adiponectin, resistin, tumor necrosis factor-α, retinol binding protein-4, visfatin, interleukin-6 and other interleukins, and angiopoietin-like-4. The discovery of these adipokines is too recent for us to have a full picture of their many functions. Undoubtedly, this list is incomplete; more hormones will likely be discovered.

The absence or paucity of adipose tissue, a syndrome known as lipodystrophy, leads to many metabolic abnormalities, including diabetes mellitus. Patients with lipodystrophy have abnormally low levels of leptin. Treatment of these patients with recombinant leptin largely ameliorates their metabolic disorder, emphasizing the importance of leptin in whole body metabolic homeostasis. Mutations at several distinct loci cause human partial lipodystrophy syndromes. Robert Hegele and his coworkers will review the genetic basis for these mutations, the clinical and biochemical phenotypes associated with these disorders, the diversity of clinical phenotypes observed in afflicted patients, and potential treatment strategies.

In addition to hormonal signals released into the bloodstream, adipose tissue is in two-way communication with the central nervous system. The areas of the brain responsible for these processes have not yet been mapped. The signaling molecules are only beginning to be identified. Timothy Bartness will discuss the relationship between photoperiod and obesity and what it teaches us about the neural circuits to adipose tissue. He will review the evidence for sympathetic nervous system innervation of white adipose tissue and offer a hypothesis for the control of body fat through efferent and afferent innervations of white adipose tissue; this hypothesis is an alternative to the control of body fat by circulating factors.

Adipose tissue is the most important storage organ for triglyceride. Excess triglyceride in adipose tissue is a hallmark of obesity, but is not per se a pathological state at the level of the adipocyte. However, excess triglyceride in myocytes, hepatocytes, or β-cells is associated with insulin resistance and cellular pathology. Whether the triglyceride is a cause or a consequence of these problems is still under question. However, the partitioning of lipid between adipose tissue and other tissues is clearly important, a topic that will be addressed by Antonio Vidal-Puig and Jaswinder Sethi.

Even the lowly fat droplet has had a wonderful decade and has emerged with new respect. This emergence began with the discovery of perilipin, a protein associated with the fat droplet. When lipolysis is stimulated in adipocytes, perilipin is phosphorylated, causing it to be released from the lipid droplet. This finding resolves a longstanding paradox: stimulation of lipolysis is far higher than the stimulation of hormone-sensitive lipase by its phosphorylation. Now, the biochemistry textbooks need to be corrected to indicate that the phosphorylation of perilipin, rather than the phosphorylation of hormone-sensitive lipase, is an important step regulating adipose tissue lipolysis, together with the activation of the newly discovered adipose triglyceride lipase. Just as leptin led the way to the discovery of additional adipokines, there are numerous proteins associated with lipid droplets, and their role in lipid metabolism is just beginning to be elucidated. This area will be reviewed by Dawn Brasaemle. She will describe the structural and regulatory roles of fat droplet-associated proteins and their relationship to lipases.

Adipocytes exert tight control over fatty acid flux and glucose transport. A large body of work attributes this control to caveolae. Paul Pilch will review the possible functions of caveolae, with an emphasis on their role in regulating fatty acid flux. He will also discuss some of the more controversial aspects of caveolae, some of which center on the technology that people use for their isolation and study.

In recent years, evidence has accrued showing that obesity is accompanied by an inflammatory response in adipose tissue. This response has major implications for insulin signaling and the endocrine functions of adipocytes. Gokhan Hotamisligil and Margaret Gregor will review

DOI 10.1194/jlr.E700001-JLR200

this topic, discussing inflammatory signaling and insulin action, molecular sensors coordinating the inflammatory responses in adipose tissue, the interface between nutrient sensing and the immune response, and the role of the endoplasmic reticulum in metabolic diseases. He will also discuss some of the therapeutic implications of these new insights.

Alan D. Attie
Associate Editor