thematic review series

Introduction to the Thematic Review Series: Adipose Biology

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The incidence of obesity has increased at an alarming rate for the past 20 years. The rapidly growing obesity epidemic is of serious concern as excess adiposity confers significant risk for developing numerous chronic disorders, including type 2 diabetes, cardiovascular disease, and cancer. As a result, there is an urgent medical and economic need to understand all aspects of adipocyte biology. The four review articles in this series address important aspects of adipose tissue physiology, including how adipocytes communicate with the rest of the body, how adipose tissue expands in obesity, and how adipose tissue dysfunction in adults can impact physiology.

Until the late 20th century, the view of adipocytes, and adipose tissue as a whole, was quite simplistic. White fat cells represent the principal site of energy storage, containing a single large lipid droplet and the enzymatic machinery to both synthesize and hydrolyze triglycerides. Thermogenic brown and beige adipocytes are specialized to dissipate chemical energy in the form of heat and likely evolved to protect mammals from hypothermia. During the mid-1990s, this view changed with the realization that adipocytes are endocrine cells that produce various hormones and cytokines that coordinate systemic responses. Two of the most notable "adipokines" identified during this time are leptin and adiponectin. Leptin functions centrally to suppress food intake and peripherally to enhance lipid metabolism. Adiponectin is a potent insulin sensitizer that influences several aspects of glucose and lipid metabolism. Today, it is becoming increasingly clear that adipose tissue invokes a variety of signaling mechanisms to communicate with surrounding organs. In this review series, Funcke and Scherer provide a comprehensive overview of newly described adipokines, including lipids, proteins, and metabolites, and the emerging data on the role of noncoding RNAs and extracellular vesicles. Despite the considerable progress made over the past 25 years, it is evident that we have only scratched the surface of the adipocyte secretome, the mechanisms by which white and brown adipocytes collaborate with neighboring tissues to coordinate systemic metabolism, and the target tissues for adipose-derived signaling molecules.

Our view of adipose tissue was also changed fundamentally by the realization that white adipose tissue is a dynamic immunological organ, where immune cells interact with adipocytes to coordinate local and systemic adaptations to changing environmental and physiological conditions. Focus was initially placed on the importance of pro-inflammatory macrophages and their potential contribution to the development of insulin resistance in obesity. Today, it is clear that the cast of immunological characters in adipose tissue is quite diverse and that the importance of these various immune cell populations goes well beyond the maladaptive response to chronic caloric excess. In the review by Bolus and Hasty, the authors highlight the involvement of the innate immune system in maintaining healthy adipose tissue homeostasis, with an emphasis on the role of anti-inflammatory macrophages, eosinophils, and innate lymphoid type 2 cells.

Another overly simplistic historical view of adipose tissues is that white adipocytes are essentially homogeneous. Several lines of evidence have emerged in the past 10–15 years to support the idea that anatomically distinct adipose depots represent distinct "mini-organs" that differentially contribute to nutrient homeostasis. The issue of white adipose tissue heterogeneity is of great clinical significance as the anatomical distribution of adipose tissue is one of best predictors of metabolic health in obesity. Obese individuals who preferentially expand visceral adipose tissue depots are at a greater risk for developing insulin resistance and cardiovascular disease than those who accumulate adipose tissue in the subcutaneous regions. Importantly, how adipose tissue distribution is regulated is still not entirely clear. There is a tremendous sexual dimorphism to body fat distribution. Sex hormones undoubtedly play a key role in controlling subcutaneous versus visceral adipose tissue accumulation. Recent genome-wide association studies now point to genetic variance as a determinant of fat tissue distribution. In the accompanying review by Clegg and colleagues, the authors discuss the importance of sex hormones, aging, and genetic variance in the regulation of body fat distribution. Understanding the hormonal and

DOI https://doi.org/10.1194/jlr.IN119000337

genetic determinants of adipose distribution will ultimately give insight into the developmental origin and unique functional properties of anatomically distinct adipocytes. Importantly, such insight will likely also reveal mechanisms driving obesity-related comorbidities.

Efforts to uncouple obesity and insulin resistance will ultimately depend on a better understanding of the exact nature of insulin resistance itself. In the review by James and colleagues, the authors examine the evidence regarding mechanisms leading to insulin resistance at the level of the adipose tissue and skeletal muscle. The authors emphasize the importance of intracellular stress pathways, particularly oxidative stress, in the impairment of glucose uptake in these tissues, and how this ultimately leads to systemic insulin resistance.

From this review series, it is our hope that readers will appreciate that adipocytes, and adipose tissue as a whole, are far more complex than previously imagined. It is clear that we have only begun to understand the ways in which adipose tissue can respond to changing environmental conditions and impact normal physiology and the development of disease. Understanding the complexity of adipose tissue can be a daunting task; however, emerging from this may be new opportunities to develop therapeutics for metabolic disease.