Trends in Cell Biology

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Review

Microenvironmental Control of Adipocyte Fate and Function

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The properties of tissue-specific microenvironments vary widely in the human body and demonstrably influence the structure and function of many cell types. Adipocytes are no exception, responding to cues in specialized niches to perform vital metabolic and endocrine functions. The adipose microenvironment is remodeled during tissue expansion to maintain the structural and functional integrity of the tissue and disrupted remodeling in obesity contributes to the progression of metabolic syndrome, breast cancer, and other malignancies. The increasing incidence of these obesity-related diseases and the recent focus on improved *in vitro* models of human tissue biology underscore growing interest in the regulatory role of adipocyte microenvironments in health and disease.

Adipose Depots and Functions

Adipose tissue is distributed over multiple subcutaneous and visceral depots, typically accounting for 15–30% of total human body weight [1]. Although plasticity between canonical phenotypes is observed [2,3], adipose tissue is generally considered either 'white', characterized by adipocytes with a single lipid droplet for efficient energy storage, or 'brown', characterized by adipocytes with multiple lipid droplets, numerous enlarged mitochondria expressing *UCP1* for uncoupled oxidative phosphorylation and nonshivering thermogenesis, and increased vasculature for heat dissipation [4,5]. In adult humans, most adipose is white, while brown adipose is present in periscapular and perispinal depots [6]. Human perivascular fat may also contain brown adipocytes [7], which, in mice, help control arterial blood pressure and temperature [8,9]. All adipose types secrete hormones to regulate systemic metabolism [10,11] and, at least in the case of white adipose depots, absorb mechanical shock to protect wear-prone tissues [12], and provide insulation to maintain body temperature [13]. The adipose microenvironment both supports and modulates adipocytes in the execution of these functions by providing regulatory cues in the forms of mechanical stimulation [14], mono- and heterotypic cell–cell interactions [15], nutrient availability [16], and interaction with the extracellular matrix [17] (Figure 1). In this review, we discuss how microenvironmental cues are transduced in adipose tissue and the functional implications of altered adipocyte microenvironments associated with obesity and adipose-related diseases. Less is known about brown adipose in humans; therefore, of necessity, we focus on the predominant white adipocyte and add observations in brown adipocytes where possible.

The Developing Adipocyte Niche

Lineage-tracing experiments in animals indicate that different adipose depots, and sometimes even different adipocytes within the same depot, arise from a variety of mesenchymal precursors of neural crest or mesodermal origin [18–20]. Brown adipocytes are derived from progenitors expressing Myogenic Factor 5 that also have the potential to form skeletal muscle [21]. The complete set of white adipose precursors has not been fully characterized, but includes

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Subcutaneous and visceral adipose depots are innervated, vascularized endocrine organs comprising multipotent progenitor cells and differentiated adipocytes.

Brown adipocytes differ from white adipocytes in their morphology, functional capacities, and depot locations, but 'beige' or 'brite' adipocytes, which share characteristics of both white and brown adipocytes, are found in some white and brown depots.

Adipocytes can expand several-thousand fold in size during cellular maturation and are electrically and metabolically coupled by gap junctions.

Biophysical cues from the microenvironment modulate adipocyte differentiation, growth, and function.

Altered adipocyte microenvironments in obesity are associated with type 2 diabetes mellitus, breast cancer, and other diseases, suggesting that microenvironmental factors in adipose tissue can be pathogenic.

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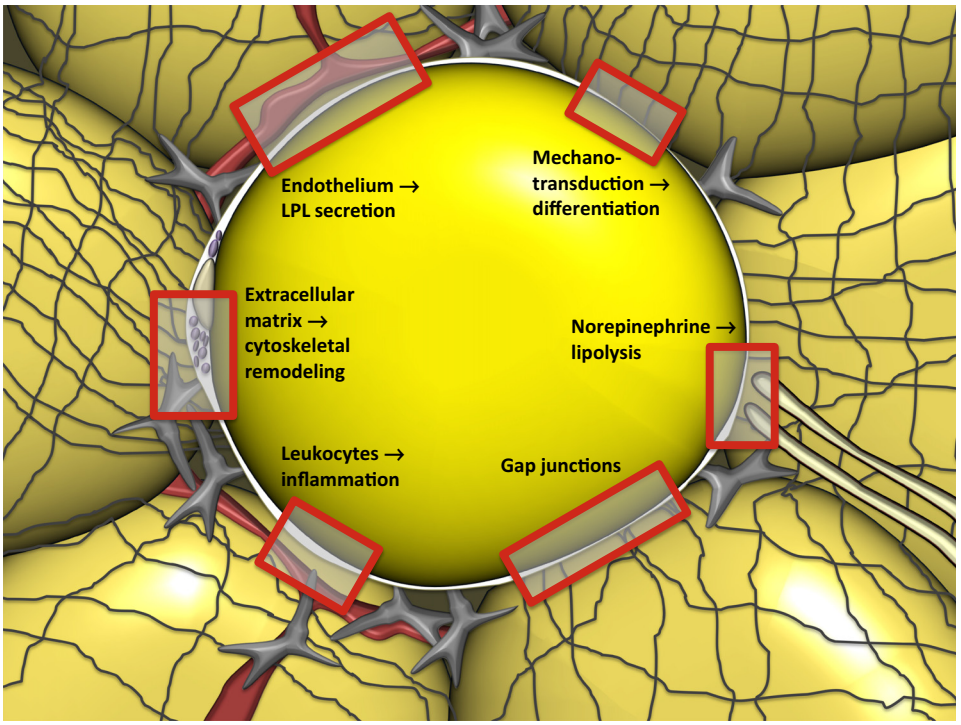

Figure 1. Regulatory Cues in the Adipocyte Niche. The contents (yellow sphere, lipid droplet; gray triangle, nucleus; purple ovals, mitochondria; white circle, cytosol), extracellular matrix (gray lines) and surrounding cell types (gold spheres, white adipocytes; gray stars, preadipocytes; crimson tubes, capillaries; cream tubes, nerves) of a white adipocyte are depicted. Red boxes represent membrane sections where regulatory cues from the microenvironment are sensed. Abbreviation: LPL, lipoprotein lipase.

multipotent mural cells expressing the zinc-finger transcription factor Zfp423 [22]. Despite arising from disparate lineages, a common microenvironment supports adipose development. Preceding adipogenesis in humans, vascularization of loose connective tissue promotes the migration and aggregation of mesenchymal cells and their differentiation into preadipocytes [23]. Lipid-bearing adipocytes appear in subcutaneous and visceral adipose depots by the end of the second trimester and variably expand from the 15-μm diameter preadipocyte up to 80 μm by birth [24]. Innervation of adipose tissue also follows inductive signals from blood vessels, but the exact developmental stages when neural projections reach different fat depots have not yet been characterized and may occur postnatally [25]. After birth, adipose also forms and progressively dominates in bone marrow, although little is known about its function [26]. Into adulthood, visceral and subcutaneous adipose depots grow at variable rates dependent upon sex hormones, nutrition, and other factors, reviewed previously [27,28].

Adipocyte Interactions with the Extracellular Matrix

Typical of the loose areolar connective tissue in which it develops, adipose is supported by an isotropic matrix of collagen and elastic fibers. Extracellular fibronectin and laminin form networks with collagen fibers [29] and provide attachment points for integrins anchored in the adipocyte membrane [30] (Figure 2). Integrins are heterodimers with alpha and beta subunits, the combination of which dictates ligand specificity [31]. Similar to receptors for paracrine signals, integrins transduce cues from the extracellular matrix to regulate gene expression and function. During adipogenesis, alpha integrin expression shifts from predominantly alpha5 in preadipocytes to alpha6 in mature adipocytes, signifying release from alpha5-binding fibronectin and