Overview

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Anatomy and Physiology of Fat Tissue

Adipose tissue has evolved into a highly specialized tissue for storing energy in the form of triglycerides (TGs, also called triacylglycerols, or "fat"). It is heterogeneous in cellular composition, location, and function – reflecting its complex role in normal physiology and disease [1]. It is comprised not only of different types of adipocytes (ranging from white to brown) but also other non-adipocyte cell types (such as stromal vascular and immune cells) to form a true multicellular organ [2]. Unlike other organs, adipose tissue is distributed throughout the body where it exhibits location-specific properties. Furthermore, its functions extend well beyond its role in fat storage to a variety of other processes necessary for physiological homeostasis including energy homeostasis, immune homeostasis, and reproductive function [3]. The heterogeneity of adipose tissue is reflected by the variety of clinical disorders that result from adipose tissue dysfunction [4, 5]. Indeed, both adipose tissue excess (obesity) and deficiency (lipodystrophy) result in profound physiological impairments that promote the metabolic syndrome (see chapter "Metabolic syndrome") and cardiovascular disease (see chapter "Atherosclerotic heart disease"). Adipose tissue dysfunction or excess also contributes to a myriad of other diseases affecting virtually all organ systems including liver disease, i.e., fatty liver and cirrhosis (see chapter "Cirrhosis"); kidney disease, e.g., diabetic and hypertensive nephropathy (see chapters "Diabetes mellitus" and "Hypertension"); pulmonary disease, e.g., sleep apnea; musculoskeletal disease, i.e., arthritis (see chapters "Osteoarthritis" and "Rheumatoid arthritis") and back pain; reproductive disease, i.e., infertility; psychological disease, i.e., depression (see chapter "Major depressive disorder"); and even cancer (see chapter "Overview" under the part "Cancer") [6]. Thus, adipose tissue is not simply an inert tissue for storing fat, but a highly dynamic tissue required for health and survival. By understanding the unique characteristics of adipose tissue, can we begin to exploit its complexities to treat or prevent disease.

Fat Tissue-Specific Metabolic/ Molecular Pathways and Processes

Adipose tissue is divided into two types: white (WAT) and brown (BAT) (Fig. 1a). WAT is composed of white adipocytes characterized by large, unilocular lipid droplets and sparse mitochondria. The high ratio of fat to mitochondria gives WAT its characteristic white appearance. WAT is

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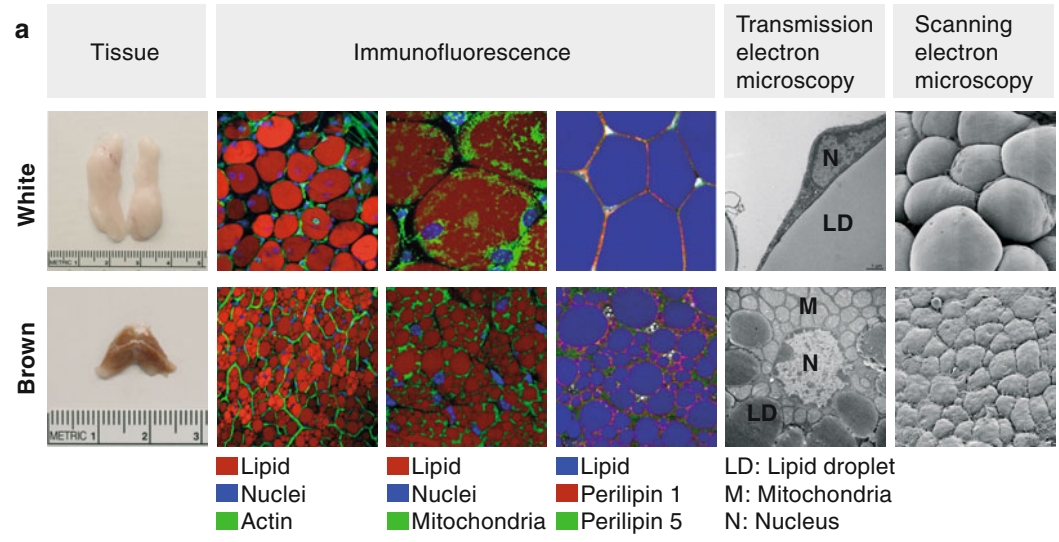

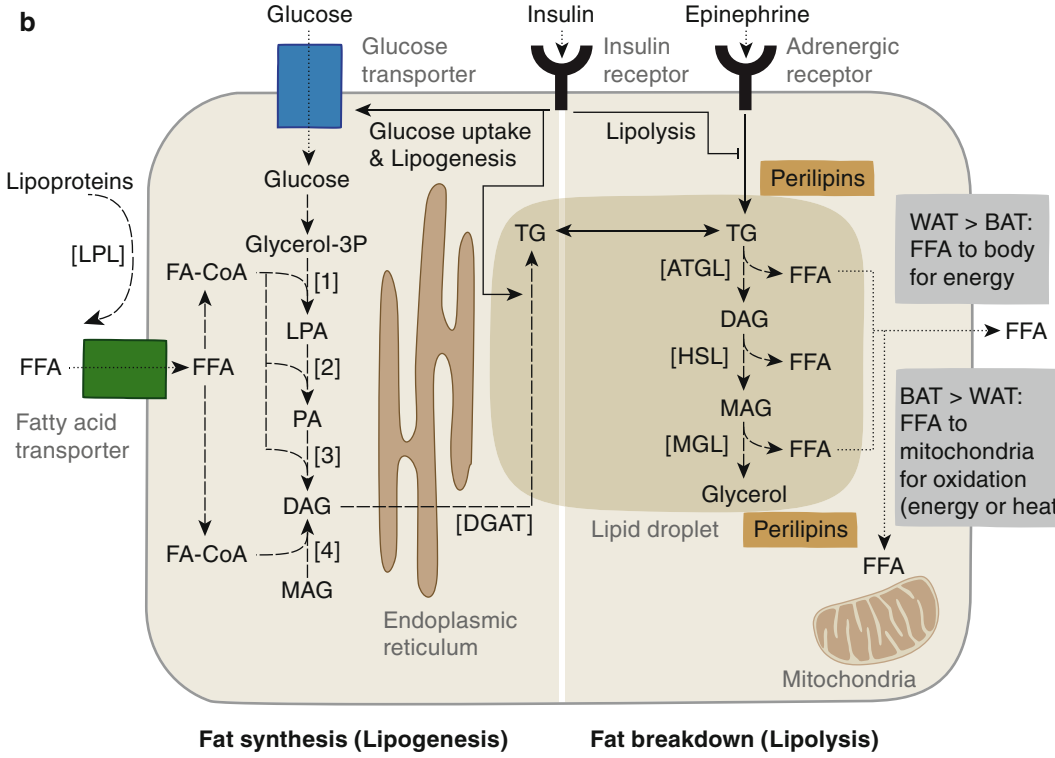

Fig. 1 Adipocyte morphology and metabolic pathways. (**a**): Distinguishing features of *white* (WAT, top panel) and *brown* (BAT, bottom panel) adipose tissue. Gross images of murine WAT and BAT (1st image). Immunofluorescence images of WAT and BAT cross sections highlighting adipocyte size (2nd image), mitochondrial content (3rd image), and lipid droplet proteins (4th image). Transmission (5th image) and scanning (6th image) electron microscopy of WAT and BAT. (**b**): Anabolic (fat synthesis or lipogenesis) and catabolic (fat breakdown or lipolysis) pathways in adipocytes. *LPL* lipoprotein lipase, *FFA* free fatty acid, *FA-CoA* fatty acyl-CoA, *Glycerol-3-P* glycerol-3-phosphate; [*1*] = glycerol-3P acyltransferase, *LPA* lysophosphatidic acid, [*2*] = LPA acyltransferase, *PA* phosphatidic acid, [*3*] = PA phosphatase, *DAG* diacylglycerol, [4] = monoacyl glycerol acyltransferase, *MAG* monoacylglycerol, *DGAT* DAG acyltransferase, *TG* triglyceride, *ATGL* adipose triglyceride lipase, *HSL* hormone-sensitive lipase, *MGL* MAG lipase (Figure courtesy of Erin E. Kershaw and Donna B. Stolz, University of Pittsburgh's Center for Biological Imaging)

located throughout the body in "depots" but is also spread within and around other tissues where it exhibits location-specific characteristics. WAT is highly specialized for storing large amounts of fat as TGs but also has several other critical functions including mechanical protection, thermal insulation, energy homeostasis, and endocrine factor production. BAT, on the other hand, is composed of brown adipocytes characterized by small, multilocular lipid droplets surrounded by copious large mitochondria. The high ratio of mitochondria to fat gives BAT its characteristic brown appearance. BAT, the presence of which has recently been confirmed in humans, is primarily located along the axial skeleton [7]. In contrast to WAT, BAT is highly specialized for fat combustion to generate heat (thermogenesis). Recently, adipocytes with mixed characteristics ("beige" adipocytes) have been identified, suggesting that specialized adipocytes may interconvert between pro-storage and pro-thermogenic phenotypes [8]. These characteristics make adipose tissue a focus of intense investigation for the treatment of obesity and metabolic disease.

Adipose tissue is exquisitely designed for the regulated storage and release of lipid substrates and possesses all the cellular machinery for both fat synthesis (lipogenesis) and fat breakdown (lipolysis, Fig. 1b). In the setting of energy excess (i.e., after a meal), energy substrates (i.e., glucose or fatty acids) enter the cell where they are converted into fatty acyl-coenzyme As (FA-CoAs). These FA-CoAs are then sequentially esterified to a glycerol backbone by acyltransferases to form TGs. TGs are stored in lipid droplets. Importantly, lipid droplets are highly dynamic organelles that are associated with a variety of lipid droplet proteins such as those of the perilipin family [9]. For example, perilipin 1 is primarily found in adipocytes where it is integrally involved in lipolysis, whereas perilipin 5 is primarily found in oxidative tissues such as BAT where it is integrally involved in lipid oxidation [9]. In the setting of increased energy demand (i.e., fasting, exercise), free fatty acids (FFA) are sequentially released from TGs by the lipolytic enzymes adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGL). In WAT, FFAs are primarily released into the systemic circulation for energy. In BAT, on the other hand, FFAs primarily enter the mitochondria for thermogenesis. These processes are critically important in adipose tissue, the main site of lipid storage and release, but are also present in virtually all cells of the body. Impaired regulation of these fundamental processes contributes to metabolic diseases.

Inside-In: Metabolites of Fat Tissue Affecting Itself

Adipose tissue consists not only of adipocytes but also a variety of other cell types including stromal cells (i.e., fibroblasts, stem cells), vascular cells (i.e., endothelial cells, smooth muscle cells), and immune cells (i.e., macrophages). These cell types interact with each other in an autocrine and paracrine manner [10]. Adipocytes and other cells within adipose tissue secrete bioactive substances known as "adipokines" (adipocyte-derived cytokines) including cytokines (interleukin 6, tumor necrosis factor α), complement-like factors (i.e., adiponectin), chemokines (i.e., monocyte chemotactic protein 1), acute phase reactants (i.e., angiotensin, plasminogen activator inhibitor 1), growth factors (i.e., vascular endothelial growth factor A), adhesion molecules (i.e., vascular cell adhesion molecule 1), hormones (i.e., leptin), and other proteins/peptides (i.e., retinol-binding protein 4, resistin). Adipocytes also express a variety of receptors for factors derived from both local and distant sources [3]. This intra- and intercellular communication influences numerous processes ranging from adipocyte metabolism and development (adipogenesis, maturation, and death) to whole adipose tissue dynamics (i.e., angiogenesis, inflammation). For example, under normal physiological circumstances, adipocyte hypertrophy promotes release of the adipocyte factors leptin and monocyte chemotactic protein 1 (MCP-1). Leptin activates receptors on adipocytes and elsewhere (i.e., the central nervous system, see chapter "Overview" under the part "Brain") to directly or indirectly restrict further adipocyte expansion. MCP-1 promotes recruitment and activation of

macrophages that dispose of excess FFAs and dead/dysfunctional adipocytes [11]. Under pathological circumstances, such as severe or prolonged nutritional oversupply, macrophage- or adipocyte-derived inflammatory factors (i.e., interleukin 6 and tumor necrosis factor α) lead to a vicious cycle of chronic inflammation, adipocyte lipolysis, and adipocyte dysfunction. This loss of adipose tissue homeostasis and the resulting changes in adipokines and fatty acids interfere with numerous metabolic processes such as insulin signaling, thereby, causing insulin resistance, glucose intolerance, and other features of the metabolic syndrome (see chapter "Metabolic syndrome") [12]. Thus, the autocrine and paracrine functions of adipose tissue are essential for maintaining adipose tissue homeostasis but can lead to disease when overwhelmed.

Inside-Out: Metabolites of Fat Tissue Affecting Other Tissues

Adipose tissue also interacts with the rest of the body to orchestrate essential physiological processes including energy homeostasis, reproductive function, inflammatory responses, and vascular hemodynamics (Fig. 2, left). Adipose tissue communicates with these distant sites through secretory factors – making it one of the largest endocrine organs in the body. Numerous adipokines have been identified as noted above and are reviewed elsewhere [3]. For example, leptin is a cytokine-like adipokine that signals the adequacy of adipocyte energy stores to the hypothalamus where it acts to decrease energy intake, increase energy expenditure, and regulate reproductive function through complex central nervous system circuits that control both neural (i.e., sympathetic and parasympathetic) and endocrine (i.e., gonadal, adrenal, and thyroid axes) output to the whole body [13]. Adiponectin is a multimeric complement-like adipokine that signals a healthy state of adipose tissue and acts at multiple sites via multiple mechanisms to improve cardiometabolic risk [14]. Conversely, the adipose tissue-derived chemokines and cytokines have systemic inflammatory effects that increase cardiometabolic risk by promoting insulin resistance, glucose intolerance (see chapter "Diabetes mellitus"), atherosclerosis (see chapter "Atherosclerotic heart disease"), and other disease processes [12]. In addition to adipokines, adipose tissue-derived FFAs serve as essential substrates for energy, signaling, and membrane synthesis throughout the body. When present in excess, however, FFAs accumulate in non-adipose tissues where they cause lipid-induced toxicity. This "lipotoxicity" contributes to insulin resistance, diabetes, dyslipidemia, and other features of the metabolic syndrome (see chapters "Hyperlipidemia", "Diabetes mellitus", and "Metabolic syndrome"). Thus, the endocrine functions of adipose tissue are essential for maintaining whole-body metabolic homeostasis.

Outside-In: Metabolites of Other Tissues Affecting Fat Tissue

Other tissues influence adipose tissue by regulating its production, distribution, metabolism, and function (Fig. 2, right). Adipocytes and other cells within adipose tissue express traditional endocrine hormone receptors (i.e., insulin, glucagon, and growth hormone receptors), nuclear hormone receptors (i.e., glucocorticoid, vitamin D, thyroid hormone, androgen, and estrogen receptors), gut hormone receptors (i.e., gastrin and glucagon-like peptide-1 receptors), cytokine receptors (i.e., leptin, interleukin 6, and tumor necrosis factor α receptors), catecholamine receptors, peptide receptors (i.e., angiotensin II receptors), and FFA receptors (i.e., Toll4 receptors) [3]. In this way, distant sites communicate with adipose tissue to integrate physiological signals. For example, in the setting of increased energy requirements, catecholamines (i.e., epinephrine) from the central nervous system or adrenal medulla act on adipocyte adrenergic receptors to stimulate lipolysis (Fig. 1b). Conversely, in the setting of increased energy availability, insulin from the pancreas (see chapter "Overview" under the part "Pancreas") acts on adipocyte insulin receptors to facilitate glucose uptake and fat synthesis while simultaneously inhibiting fat breakdown and promoting

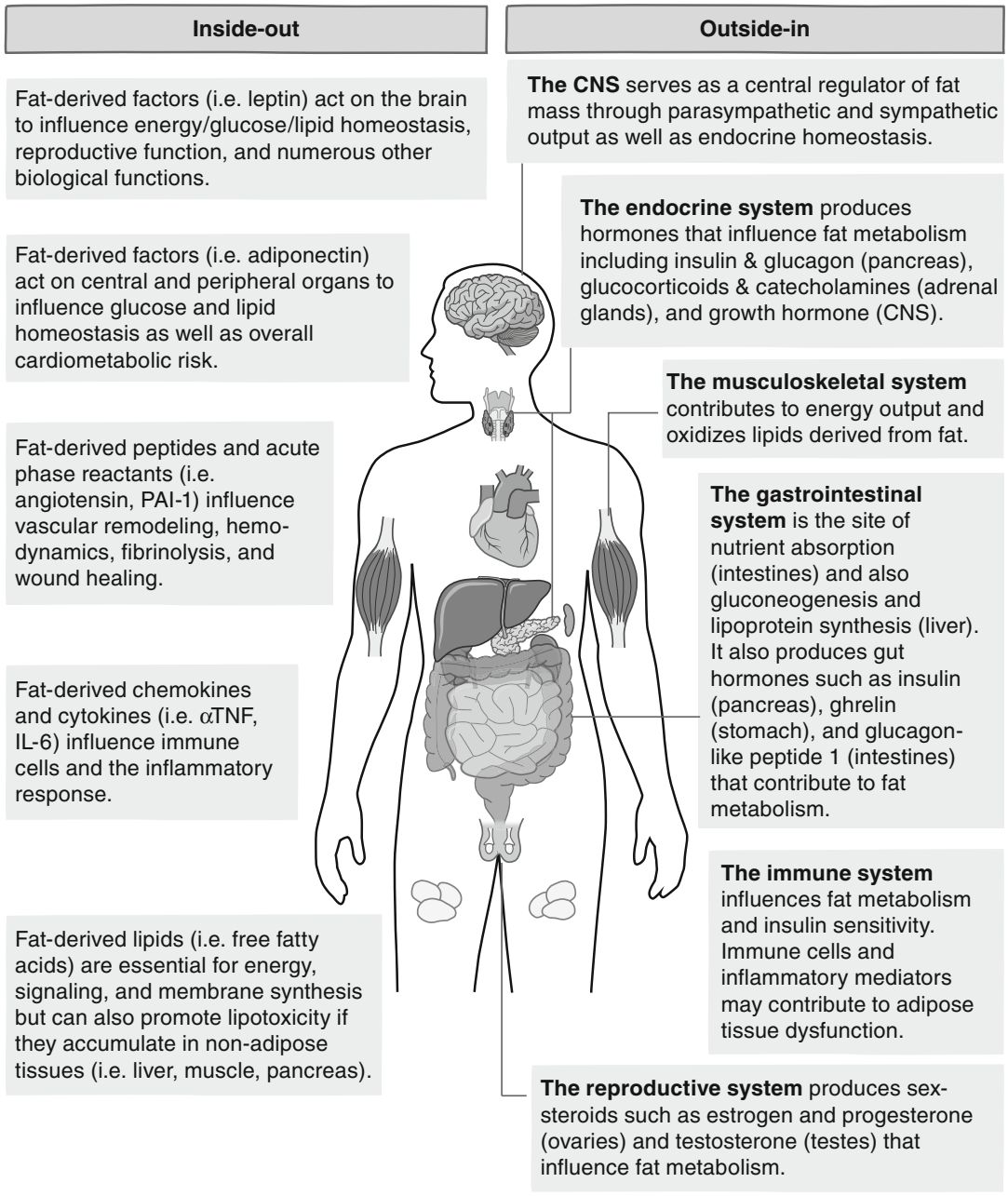

Fig. 2 Interactions between adipose tissue and other tissues (Figure courtesy of Erin E. Kershaw and Gianna Paniagua)

adipogenesis (Fig. 1b). Interestingly, just as the spectrum of adipocyte-secreted factors varies across adipose tissue depots, so does adipose tissue responsiveness to systemic signals [15]. For example, subcutaneous and breast adipose tissue is particularly responsive to estrogens from the ovaries, whereas visceral adipose tissue is particularly responsive to glucocorticoids from the adrenal glands. On the other hand, BAT is particularly responsive to temperature (i.e., increasing thermogenesis in response to cold). Thus, adipose tissue is a highly adaptive tissue that responds to both global and local needs of the body.

The body is exquisitely designed to maintain energy homeostasis and adiposity, and yet the global epidemic of obesity and obesity-associated diseases continues to grow [16, 17]. Numerous intrinsic and extrinsic signals influence fat mass and function, either directly by acting on adipocytes themselves or indirectly by influencing other peripheral or central organs. Adipose tissue and the central nervous system integrate these signals and communicate with each other via complex neural and hormonal networks to control energy homeostasis and other physiological processes [16]. Generally, genetic and environmental factors have been considered to be the primary determinants of fat mass. Indeed, recent genome-wide association studies (GWAS) suggest that as much as 70 % of obesity may be attributed to genetic factors [18]. The main environmental factors contributing to fat mass are diet (energy intake) and exercise (energy expenditure). Lifestyle modification, either by decreasing the former or increasing the latter, promotes weight loss by decreasing fat synthesis/storage and/or increasing fat breakdown/oxidation and subsequently improves features of the metabolic syndrome (see chapter "Metabolic syndrome") [19]. A variety of other factors have also been implicated in adipose tissue dysfunction including microorganisms, epigenetics, sleep patterns, pharmacological agents, and endocrine-disrupting chemicals [20, 21]. However, despite the tremendous progress in understanding adipose tissue biology, many questions remain unanswered.

Final Remarks

In summary, adipose tissue ("fat") is a highly complex, heterogeneous, and dynamic organ. Thus, multiple factors (both intrinsic and extrinsic) contribute to its molecular, cellular, and physiological heterogeneity. Only by understanding these factors can we determine how to target them for therapeutic benefit in the fight against the growing epidemic of obesity, metabolic syndrome, and cardiovascular disease.

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