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Depot-Dependent Biology of Human Adipose Tissues and Metabolic Health

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Keywords

adipose, adipocytes, cell composition, fat distribution, metabolism, endocrine

Abstract

Body shape influences risk of cardio-metabolic diseases, independent of obesity. An apple shape, defined by larger waist circumference, is associated with higher risk. Higher amounts of visceral and/or subcutaneous adipose tissues contribute to whole-body metabolic risk. In contrast, a pear shape, with higher fat storage in gluteal-femoral depots, exerts protective effects on metabolic health, independent of sex and total adiposity. Differences in growth, remodeling, metabolism, and endocrine functions of adipose depots contribute to these associations. Innervation, blood supply, and sensitivity to endocrine signals and local secreted factors contribute to depot variations in function. At the systemic level, adipose tissues influence metabolic health by secreting adipokines and other factors packaged in extracellular vesicles. Depot differences in the production of secreted factors and their contributions to risk for developing obesity-related metabolic diseases hold promise for understanding the role of body shape in metabolic health.

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1. INTRODUCTION

Body fat is stored in anatomically distinct adipose tissues, commonly referred to as depots. Collectively, these depots compose the adipose organ as defined by Cinti and colleagues (48). The relative size of the major adipose depots determines body shape. An apple shape is associated with higher waist circumference. It is driven by higher amounts of fat stored in either abdominal subcutaneous adipose tissue (ASAT) or visceral adipose tissue (VAT) depots. A pear shape is due to greater fat stored in gluteal subcutaneous adipose tissue (GSAT) or femoral subcutaneous adipose tissue (FSAT) fat depots of the lower body, i.e., hips and thighs (42, 127).

A larger waist size is recognized as deleterious for metabolic health. Strong clinical and epidemiological evidence shows that upper body fat distribution, with increased visceral and subcutaneous fat, promotes risk for type 2 diabetes (T2D). In contrast, higher amounts of lower body fat (stored in GSAT or FSAT) exert protective effects on metabolic health (42, 60, 135). Understanding the mechanisms that influence the growth and function of each of these depots is therefore of paramount importance for understanding the health effects of fat distribution.

Adipose tissues consist of multiple cell types, including adipocytes, adipose progenitors (APs), structural fibroblasts, endothelial cells, nerves, and pericytes. They reside in an extracellular matrix (ECM) that differs among the depots and influences adipose tissue function in a depot-dependent manner. Knowledge of depot differences in metabolic capacity, growth and remodeling capacity, secretory function, ECM, and cell composition is rapidly evolving (35). Here we review recent advances in knowledge about the cellular and molecular underpinnings of adipose depot–specific

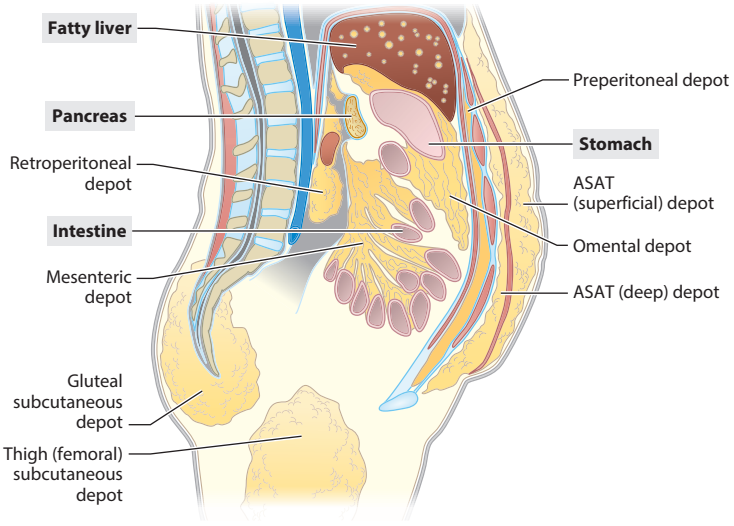

Figure 1

Adipose tissue depot localization. The majority of studies are performed on ASAT above the fascia (superficial) and omental (visceral adipose tissue) depots. The lower body adipose tissue depots include the gluteal and femoral (thigh), often referred to as gluteal-femoral adipose tissues. Abbreviation: ASAT, abdominal subcutaneous adipose tissue. Figure adapted from Reference 66.

growth and function with a particular focus on (*a*) genetic and epigenetic determinants of fat distribution, (*b*) metabolic function and cell composition differences between adipose tissue depots, (*c*) the importance of the adipose ECM (matrisome) in adipose tissue expansion, (*d*) endocrine and local (paracrine) interactions with nearby organs, and (*e*) the newly appreciated roles of extracellular vesicles (EVs) in organ cross talk (85).

2. ADIPOSE TISSUE DEPOTS AND METABOLIC HEALTH

As illustrated in **Figure 1**, upper body fat includes visceral fat, i.e., intra-abdominal adipose depots associated with the digestive tract, named omental and mesenteric. The subcutaneous depots are mainly divided into upper abdominal (ASAT) and lower body, including GSAT, FSAT, and gluteal-femoral subcutaneous adipose tissue (GFSAT). GSAT is usually sampled posteriorly and expresses the posterior developmental gene HOXC13 (e.g., 71, 80). Femoral (thigh) is usually sampled anteriorly (16, 80). Gluteal-femoral is sampled from a more lateral site that includes both depots and as expected does express HOXC13 (30, 71).

Strong clinical and epidemiological evidence shows that upper body fat distribution, with increased visceral and subcutaneous fat, promotes risk for T2D, metabolic disease (1, 75), and cardiovascular disease (135). In contrast, higher amounts of lower body fat (gluteal and thigh depots) exert protective effects (42, 60, 135). Studies of body shape and metabolic health in humans use abdominal fat as assessed by waist circumference or imaging techniques like magnetic resonance imaging (MRI) or computed tomography (CT) to assess only central adiposity.

Agrawal et al.'s (1) analysis of more than 40,000 whole-body MRI images from the UK Biobank reveals that lower body gluteal-femoral fat exerts a body mass index (BMI)-independent protective effect on cardiometabolic risk. The strength of this study is that the impacts of VAT, ASAT, and GFSAT were each assessed. Furthermore, Lindgren and colleagues (9) combined

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data from exome-wide genetic, transcriptome-level, and in vitro human fat cell culture studies to confirm the roles of several candidate genes implicated in specific pathways regulating fat distribution. These studies support the value of such integrative approaches for understanding the influence of different adipose tissues and fat distribution patterns on cardiometabolic risk.

VAT influences metabolic health via its proximity with other organs. As we reviewed recently (42), the visceral depots drain directly into the portal vein and thus exert strong effects on hepatic metabolism and the development of an important aspect of metabolic syndrome, hepatic steatosis. ASAT is a large depot that has the major impact on systemic free fatty acid (FA) flux (91). If the rate of appearance of FA from ASAT exceeds the ability of other tissues in the body, especially muscle, to oxidize this important fuel (65), FAs return to the liver where they are incorporated into triacylglycerides (TAGs), contributing to hepatosteatosis. The increase of circulating TAG leads to higher risk of peripheral insulin resistance. With time, excess FA availability leads to ectopic fat deposition in nonadipose tissues that are not able to store it safely. **Figure 1** shows how each adipose depot can contribute to interindividual variations in systemic metabolism and hence cardiometabolic risk as well as T2D and atherosclerosis.

3. GENETIC CONTROL OF FAT DISTRIBUTION

Both level of obesity and fat distribution are controlled by genetic factors (14). Specifically, waist-to-hip ratio (WHR) is heritable with a range from 22% to 61% even after accounting for obesity (125, 129). Genome-wide association studies identified hundreds of loci to be associated with proximal measurements of body fat distribution such as WHR (53, 151) and hip and waist circumference (53, 151). A genome-wide cross-phenotype meta-analysis identified genes associated with fat distribution and pathways that uncouple the association between obesity level and cardiometabolic risk (59). These included genes that are key players in adipocyte development, metabolism, and inflammation. Sex-stratified analyses of those analyses revealed that fat distribution genetic associations strongly differ between the sexes, with WHR-associated loci displaying stronger effects in women (121, 131). These results from cohorts of European ancestry have been now replicated in various ethnic populations (4, 56). Furthermore, a genetic predisposition to higher WHR adjusted for BMI is associated with increased risk of T2D and coronary heart disease. These findings suggest that the genetic background of fat distribution is involved in the prevalence of metabolic syndrome, which can elevate BMI, waist circumference, hyperlipidemia, and hypertension (33).

Genetic studies have also identified single nucleotide polymorphisms that are associated with a favorable body fat distribution (157) and with a lower cardiometabolic risk (95). Interestingly, genes near loci for fat distribution are enriched for expression in adipose tissue. For instance, the loci containing HOTAIR, HOXC13, and miR196a showed the highest logarithm of the odds score for WHR association (155), these three genes being highly expressed in GFSAT and seemingly involved in the lower body–specific adipose tissue (AT) functions (30, 55). Similar work revealed an association between RSPO3 genetic variants with $WHR_{BMI\text{-}adj}$ and with RSPO3 AT gene expression (93). Overall, fat depot–specific gene expression, particularly between upper and lower body fat depot, provides additional support for the genetic origin of fat distribution (45, 71, 120). However, polymorphisms so far described in the literature can explain only a small proportion of phenotypic variance and heritability in fat distribution. Thus, it is most likely that environmental factors, likely including but not limited to diet and physical activity, also contribute to interindividual differences in fat distribution.

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4. DEPOT DIFFERENCES IN GENE EXPRESSION

Gene expression differences between the two major visceral depots, omental and mesenteric, have been reported (100, 161). As briefly mentioned in the previous paragraph, ASAT and GFSAT are also characterized by a distinct transcriptional profile. Multiple studies identified homeobox genes as the most differentially expressed genes between both depots (71, 120). Advances in sequencing methods in the past 10 years helped to extend those differences into noncoding RNA. Our initial discovery highlighted the importance of a region on chromosome 12 (HOTAIR/HOXC13/miR196a). The lncRNA HOTAIR was found expressed at higher levels in the GFSAT versus ASAT adipocytes and preadipocytes (30) of both apple and pear shapes in a binary pattern. Using a model of overexpression and downregulation of HOTAIR in, respectively, ASAT and GFSAT preadipocytes, we showed that HOTAIR modulation leads to a massive change of gene expression accompanied by chromatin reorganization as assessed by assay for transposase-accessible chromatin using sequencing (ATAC-seq) (36). Complementary to our work, Pinnick's group showed that HOTAIR modulates adipocyte transcriptome via epigenetic regulation (81). Functionally, we also showed that the overexpression of mir196a, microRNA upregulated in GSAT in human preadipocytes, regulated the expression of HOX genes (30). Another group showed that miR196a regulated genes coding for ECM components (55). Finally, we provided new evidence that the transcription factor CTCF (CCCTC-binding factor) plays a key role in differential regulation of SAT progenitor gene expression and may influence the development of apple versus pear shape (37). A still debatable question is the intrinsic nature of those differences.

5. EVIDENCE FOR EPIGENETIC EFFECTS ON FAT DISTRIBUTION

Depot differences in gene expression are maintained in isolated preadipocytes prepared from the same individual at the same time. This observation suggests an underlying epigenetic regulation of depot-specific gene expression. Indeed, epigenetic modifications, introducing mitotically and meiotically heritable marks on the chromatin, such as DNA methylation, histone posttranslational modifications, and small and long noncoding RNA-associated gene silencing (132), modify long-term gene expression, and could be the adaptative mechanism to environmental changes.

The first study implying the role of epigenetics in fat distribution was conducted by Blumfield et al. in 2012 (13). These authors revealed an association between maternal nutrition during pregnancy and intrauterine development of fetal body composition and fat distribution later in life. They also showed that nutritional intervention in the mother may change the deleterious fat distribution.

Methodological improvements have contributed to recent advancements in the epigenetic field. Several studies investigated genome-wide DNA methylation and its association with obesity or related phenotypes in human tissues (61, 128, 137). DNA methylation at specific genes such as IRS1 in ASAT and omental AT (124), LPL, ADIPOQ, PPARG in ASAT (31), and SSPN in ASAT (72) have been shown to correlate with regional fat distribution and to be involved in visceral fat accumulation. Using a methylome array, Pinnick et al. (120) showed differential DNA methylation in abdominal and gluteal fat depots are associated with differential gene expression in lower- and upper-body obese subjects. The same type of analysis performed by Gehrke et al. (45) confirms that DNA methylation at the promoter of developmental genes drives adipose tissue depot-specific gene expression.

Chromatin structure and accessibility are also crucial for the regulation of gene expression. DNA methylation differences and at lipid storage genes between abdominal and gluteal-femoral adipocytes are associated with chromatin accessibility differences (28). This study also revealed a unique transcriptome associated with specific chromatin openness in abdominal

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and gluteal-femoral fat between women with upper and lower obesity, strongly suggesting an epigenetic contribution to the regulation of genes involved in interindividual body fat distribution variation (28). Additional work using only isolated adipocytes instead of whole tissue highlighted key epigenetic differences at developmental genes between adipocytes isolated from visceral and subcutaneous depots (15). Importantly, those studies are performed on whole-tissue or nondividing cells (mature adipocytes), and hence these modifications would not be heritable. To address this issue, we recently performed a more in-depth analysis of the AT transcriptome and epigenome of cultured preadipocytes from ABD and gluteal-femoral (GF) depots of apple- and pear-shaped women (51). We identified twice as many genes upregulated in the GF compared with the ABD cells. In addition, the cells originating from GF AT of apple-shaped women have twice as many opened chromatin regions (identified by ATAC-seq) relative to the cells of pear-shaped women. These opened regions are highly susceptible to chromatin modification, including DNA methylation, and regulate gene expression (27). Altogether these data suggest that the depot-specific transcriptome is regulated by epigenetic mechanisms. The question of what comes first remains open. Causality studies are needed to explain the relation between fat distribution, mRNA expression, and chromatin modifications.

6. ADDITIONAL DETERMINANTS OF FAT DISTRIBUTION

In addition to genetic and epigenetic factors, the pattern of adipose tissue distribution depends on many factors, including sex, age, diet, physical activity, hormone levels, and medications (69, 156). Hormonal fluctuations are the most obvious factor influencing it. VAT and SAT masses typically increase as a child ages, in proportion to total body fat. Sexual maturation greatly influences the distribution of adipose tissue. Girls accumulate more total body fat and SAT during and after puberty, depositing fat preferentially in the gynoid and extremity regions. In contrast, pubertal and postpubertal boys deposit more fat in the abdominal region, particularly in VAT depots (60, 90).

Body fat distribution also changes according to menopausal status; SAT areas are higher in premenopausal women, whereas VAT areas are higher in postmenopausal women. One explanation could be the effect of estrogen on adipogenesis. Estrogen participates to increase GFSAT expansion in women due to higher expression of the estrogen receptor in the GF adipose precursor cells (82) while inhibiting VAT accumulation. In accordance, during menopause when estrogen levels decrease, fat distribution changes. Knowledge on the role of male hormones is currently limited to the effect of testosterone on adipogenesis (144) and merits further investigation.

Karastergiou & Fried (70) described sex differences between ASAT and GFSAT functions. In summary, ASAT and GSAT adipocytes of women compared with those of men are more sensitive to insulin and, in the case of abdominal cells, to adrenergic agonists (58); the production of key adipokines, leptin, and adiponectin is higher in female adipose tissues (5, 24); and lower body fat responds to excess energy intake mainly with adipocyte hyperplasia, in contrast to the hypertrophic response seen in ASAT, and this is particularly the case in women (146). Important studies using adipose samples from transgender individuals showed that sex differences in the amount of subcutaneous fat, adipocyte size, and in vitro basal lipolytic activity could be largely reversed by cross-sex hormone treatment in adult subjects (32). These studies highlighted the key implications of sex hormones in fat distribution and the importance of comparing well-defined age groups.

Ethnicity could also influence differential AT depots development. VAT tends to be higher in individuals of European origin and Hispanic youth, whereas SAT is typically higher in African American youth. East Asians (Chinese, Japanese, and Koreans) have the largest accumulation of

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VAT but the lowest accumulation of deep SAT (111). The genetic and environmental determinants of these differences remain unclear.

7. DEPOT DIFFERENCES IN METABOLIC FUNCTION

The morphology and biological function differences between ASAT and VAT have been extensively studied (11, 145). These depots differ in adipocyte morphology, lipolytic rates, and blood flow. They also differ in their proximity to other metabolic organs such as liver and intestine that could exert local effects, as well as responses to external stimuli such as steroids, sex hormones, and thiazolidinediones, drugs largely prescribed to treat T2D. Distinct molecular programs could explain the functional differences between these two depots. In fact, transcriptional signatures have been reported to differ between ASAT and VAT (46, 149). Notably, VAT is consistently characterized by higher levels of inflammatory markers (113) and decreased adiponectin secretion (102). Differences in the secretome (68) and proteomic profiles (57) of VAT and ASAT are consistent with the hypothesis that their distinct cellular and molecular mechanisms contribute to variations in insulin resistance, metabolic syndrome, and cardiovascular disease.

The differences between the SAT depots (particularly ASAT and GSAT) have been less studied. The main biological differences between upper- and lower-body SAT adipose tissues have been previously summarized (87) and could explain their different capacities. The GSAT adipocytes seem to be larger and more insulin sensitive. Studies performed by Jensen (64) using meal-derived FA tracers (^{14}C-triolein or ^{3}H-triolein) have established a positive correlation between lower-body adipose stores and efficiency of meal FA uptake in the GF depot. Regional fat depot differences of insulin-suppressed lipolysis as measured in vitro also exist (78, 134), potentially due to higher total numbers of β-adrenoceptors in the abdominal adipocytes and lower affinity properties of the α-2 adrenoceptor. Studies employing depot in vivo glycerol measurements using microdialysis have demonstrated that lean and pear-shaped women had a significant reduction in abdominal glycerol release with hyperinsulinemia, whereas apple-shaped women did not (112). FSAT glycerol release was suppressed to a similar extent following insulin stimulation in lean, apple-, and pear-shaped women (112).

Finally, the greater FFA release in ABD AT in apple-shaped women is proposed to account for greater postprandial FFA availability (49). One of our studies extended these data by showing that after a frequently sampled intravenous glucose tolerance test, pear-shaped women had the highest suppression of systemic FFA release in comparison to apple-shaped women and men (28).

8. DEPOT DIFFERENCES IN CELL COMPOSITION MAY CONTRIBUTE TO DEPOT DIFFERENCES IN FUNCTION

Adipose tissues include adipocytes, APs at varying levels of commitment toward preadipocytes, fibroblasts, endothelial cells, pericytes, nerves, and immune cells (macrophages, dendritic cells, leukocytes) (63). Recent advances in single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) have been crucial in determining the cellular heterogeneity in different AT depots and diseases (obesity, aging, metabolic syndrome). Most of the published research on adipose cell composition has focused on human SAT, only a few compared the ASAT to the VAT (usually omental), and only one reported differences between the ASAT and GFSAT (29). In this study, we showed that ASAT precursor cells are more committed to an adipocyte lineage. However, they seem to be less able to differentiate into mature adipocytes in vitro, underlining the importance of assessing the contribution of paracrine factors in the depot microenvironment to AP differentiation. **Table 1** summarizes depot differences in cell composition detected with snRNA-seq or scRNA-seq studies.

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Table 1 Main cell types identified in human ASAT and VAT (omental) by scRNA-seq or snRNA-seq method

Method	Reference	Adipocytes	Adipocyte progenitors/stem cells	Immune cells	Vascular
scRNA-seq on SVF	Vijay et al. (148)	NA	7 subsets 60% of the SVF P2.P6, P7 SAT>VAT P1, P3, P5 almost exclusively in VAT	7 subsets 34% of the SVF NK/T cells ATM Dendritic cells B cells	3 subsets 6% of the SVF
snRNA-seq on frozen AT	Emont et al. (34)	7 subsets Ad1, Ad3 (TG biosynthesis), Ad4, Ad7 SAT>VAT Ad2, Ad6 (thermogenic) exclusively in VAT	6 subsets ASPC1, ASPC4, ASPC5 SAT>VAT ASPC3, ASPC6 VAT>SAT	8 subsets Monocytes Macrophages Dendritic cells B and T lymphocytes NK cells Mast cells Neutrophils	11 subsets Blood endothelial cells, arterial, stalk and venular (6) Lymphatic endothelial cells (2) Smooth muscle cells (2) Pericytes
scRNA-seq on CD45/CD31 positive	Ferrero et al. (39)	NA	2 main subsets: ASCs[a] and preadipocytes 6 subsets of ASCs: vascular smooth muscle progenitor, mesothelial (only in omental), HHIP+, IFIT+, SFRP4+, RBP5+	NA	NA
snRNA-seq	Lazarescu et al. (84)	32% in SAT, 18% in VAT 6 subsets: Ad1 (FA and lipid metabolic processes), Ad2 (angiogenesis), Ad3 and Ad4 (immune regulation), Ad5 (ECM processes), Ad6 (only in VAT, mitochondrial, and ribosomal genes and processes)	NA	NA	NA

Abbreviations: Ad, adipocyte; ADSC, adipose-derived stem cell; APC, adipose progenitor cell; ASAT, abdominal subcutaneous adipose tissue; ASC, adipose stem cell; ATM, adipose tissue macrophage; ECM, extracellular matrix; FA, fatty acid; NA, not applicable; P, population; scRNA-seq, single-cell RNA sequencing; snRNA-seq, single-nucleus RNA sequencing; SVF, stromal vascular fraction; TG, triglyceride; VAT, visceral adipose tissue.

[a]The terms ASC, ADSC, and APC are interchangeable.

A spatial transcriptomic study, combining the recent technological advancements that allow molecular investigation on a single-cell level and cellular localization within tissue, reported three subpopulations of white mature adipocytes in ASAT displaying distinct transcriptomic signatures associated with spatial organization (7). Interestingly, the AdipoPLIN subpopulation (high expression of PLIN1 and 4) correlates with higher in vivo insulin sensitivity. Another subpopulation, AdipoSAA, is enriched for genes involved in lipid uptake and handling, and the AdipoLEP subpopulation shared common enriched pathways related to leptin synthesis/signaling and ECM remodeling. scRNA-seq technology also advanced the characterization of immune cells within AT. In this respect, scRNA-seq analysis coupled with flow cytometry using CD45+ on SVF from deep SAT identified 15 new distinct cell clusters of immune cells, including ILCs, DCs, NK cells, and proinflammatory macrophages (54). To summarize the multitude high-quality data generated over 10 years, Massier et al. (98) recently integrated newly generated single-cell, single-nucleus, and spatial transcriptomic results from human ASAT and omental AT. They identified new cell–cell interactions as well as relationships between specific cell subtypes and insulin resistance, dyslipidemia, adipocyte volume, and lipolysis upon long-term weight changes (98). These results highlight the importance of studying the depot-dependent cell composition of adipose tissues in greater numbers of metabolically well-phenotyped subjects. In this respect, Wolfrum's lab (123) leveraged snRNA-seq technology to compare cellular composition of ASAT and VAT in metabolically healthy and unhealthy obese subjects. They found remarkable changes in cellular composition for each cell type in VAT, independently of sex and adiposity, whereas the ASAT cellular landscape was mostly unchanged. Furthermore, the fraction of visceral adipocytes was higher in metabolically healthy obese individuals than in metabolically unhealthy obese individuals, suggesting the maintenance of adipocyte hyperplasia in metabolically healthy obese individuals.

A repository for single-cell data, the Human Cell Atlas Adipose Bionetwork, has been created to "support the generation of single-cell atlases of human AT as well as the development of unified approaches and consensus for cell annotation" (92, p. 875).

9. DEPOT-DEPENDENT VARIATIONS IN ADIPOSE EXPANDABILITY

Adipose tissues can expand in size over a very wide range. Increases in adipocyte size (hypertrophy) as well as number (hyperplasia) may contribute. Adipocyte hypertrophy is the main contributor to the higher fat storage in lower-body depots, GSAT and FSAT. These adipose depots efficiently store fat without becoming dysfunctional (at least for some time or to an individual threshold) (101). This higher expandability is likely to relate to a larger pool of APs that can be recruited to replace older, less functional ones, enabling more efficient fat storage (152) (**Figure 2**). This homeostatic process allows the adipocyte number to remain constant. In addition, adipose expansion involves increases in the size of adipocytes as well as an increase in their number. Using an 8-week incorporation of deuterium ($^{(2)}H$ from $^{(2)}H_2O$) into the DNA of adipocytes and preadipocytes, White et al. (153) showed that preadipocytes and adipocytes had higher formation rates in the FSAT depot relative to the ASAT depot. We also identified different degrees of preadipocyte commitment to adipogenesis in adipose-derived stem cells isolated from paired GFSAT and ASAT (29). Additional research is needed to investigate the rate of adipogenesis in the different AT depots.

Adipose tissue expansion also requires a remodeling of the ECM structure (matrisome; as reviewed below). Rates of remodeling and expansion vary among depots (88). Technical issues related to the assessment of depot mass from imaging analyses and the small number of studies that attempt to compare cell numbers in different SATs and VATs limit information available on depot differences in human adipose cellularity.

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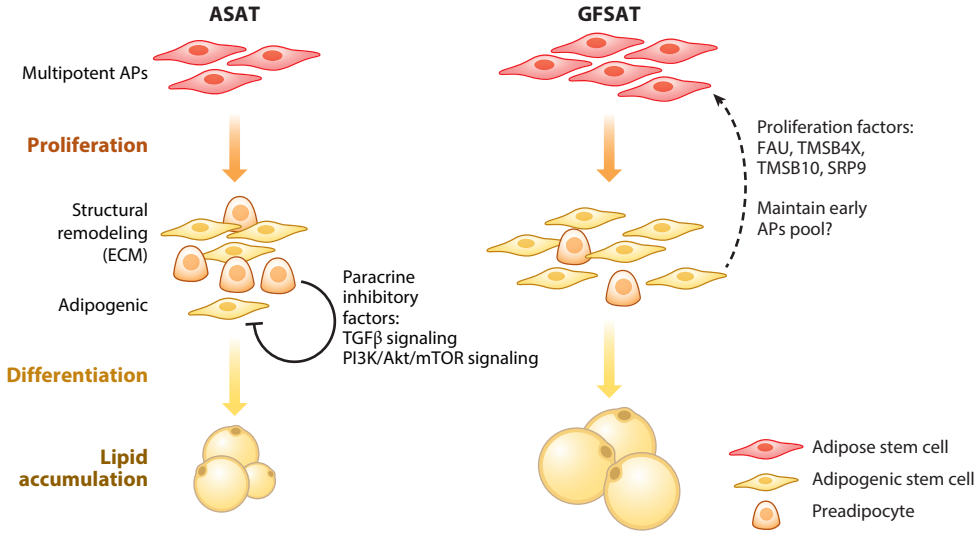

Figure 2

Identification of depot-specific AP populations by single-cell RNA sequencing using stromal vascular fraction adherent cells (38581663) and their potential impact on depot-specific fat expansion. Preadipocytes are defined as cells expressing early markers of differentiation and the two only known preadipocyte marker genes (Pref1 and znf423). Abbreviations: AP, adipose progenitor; ASAT, abdominal subcutaneous adipose tissue; ECM, extracellular matrix; GFSAT, gluteal-femoral subcutaneous adipose tissue.

10. DEPOT DIFFERENCES IN THE EXTRACELLULAR MATRIX COULD MODIFY ADIPOCYTE FUNCTION

The functions of adipocytes and other cells within adipose tissue depend strongly on the composition and properties of its ECM. Hynes & Naba (62) and Naba (108) pioneered and greatly expanded proteomic analyses of the ECM proteome (matrisome) in tissues, including adipose tissue. The core components of the matrisome modulates its structure, strength, and stiffness. These properties are modified by collagens, elastins, fibronectin, and fibrillins. The ECM also includes multiple proteoglycans that modulate growth factor binding and so-called ECM-affiliated proteins and secreted factors. The ECM contributes to depot differences in pathways of cell adhesion, migration, and proliferation, as well as the metabolism and secretory functions of adipocytes. Data support a role for the ECM in contributing to depot-specific differences in adipogenic potential and adipocyte metabolism; however, those studies are limited to animal models (105, 140).

A few studies reported that ECM composition varies among adipose depots (103, 141). These studies establish gene-level differences in the expression of ECM and ECM-related genes in visceral (omental, mesenteric) (21) and abdominal subcutaneous (71) depots. Specifically, genes that encode factors in ECM remodeling are more highly expressed in the ASAT compared with omental adipose tissue of obese individuals with a metabolically healthy phenotype (138). Insulin resistance in obesity is associated with higher levels of the ECM proteoglycan lumican in ASAT. Lumican modifies collagen I organization, impairs adipogenesis, and activates stress processes (endoplasmic reticulum and oxidative stress) in adipocytes (50). Ongoing work is examining how depot differences in the ECM affect adipose metabolism and expansion capacities (141). The importance of the ECM composition to adipocyte function and changes with obesity are demonstrated by studies of O'Rourke and colleagues (8, 17, 83). It is becoming increasingly clear that direct cross talk of the ECM and adipocytes is a major influence on adipocyte function. Dynamic

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remodeling of the ECM is necessary for maintenance of adipose tissue homeostasis (83, 97). A recent review (108) details mechanisms that mediate the assembly of the ECM and its remodeling as required for the expansion of adipose tissues. In this context, Caprio and colleagues (133) used state-of-the-art stable isotope technologies to document rates of adipogenesis, and ECM dynamics were higher in abdominal versus gluteal adipose tissues from adolescents with obesity. They concluded that depot differences may contribute to ectopic fat deposition, specifically liver steatosis as assessed by imaging, in the most insulin-resistant individuals. These results were similar to those of the Klein laboratory in adults (10). Together they emphasize that susceptibility of adipose tissues to ECM fibrosis is a key driver of metabolic dysfunction in people with obesity.

It will be important in future studies to assess how the changes in ECM could influence depot-specific growth and adipocyte function in paired subcutaneous AT. In addition, changes in ECM gene expression during the relatively early stages of experimental overfeeding (14 days) provide a dynamic model for future mechanistic studies of ECM remodeling in vivo (3). Analysis of shifts in ECM composition and structure prior to significant weight and fat gain, as has been studied in mice, are likely to be highly informative, specifically to assess depot difference fat expansion.

11. VASCULARIZATION AND INNERVATION OF ADIPOSE TISSUES

Larger adipocytes receive less vascular and neural input per cell and per unit of cell surface. Low vascularization is associated with relative hypoxia and contributes to the adipocyte dysfunction and insulin resistance in obesity (22, 41, 116, 117). Using direct measurement of oxygen tension, Smith's laboratory (117) provides direct evidence for hypoxia within the ASAT of obese humans. The magnitude of hypoxia was associated with infiltration of macrophages and a proinflammatory profile, as well as decreased production of proangiogenic molecules such as VEGF. Intriguingly, adipose tissue partial pressure was negatively correlated with fibrosis as measured by collagen 6 mRNA and positively with PPARγ1 expression. Taken together with the COL6 knockout mouse that exhibits adipocyte hypertrophy without negative metabolic consequences (74), these data suggest that hypoxia may drive adipose tissue inflammation and fibrosis.

Low innervation of adipose tissues creates a peripheral neuropathy in obesity, diabetes, and aging (12). Sympathetic nerves provide input from the brain center to modulate lipolytic rates. The current state of knowledge of sensory nerves and neuropeptides that regulate adipose tissue function have been greatly advanced and is well-reviewed by Townsend and colleagues (12). An intriguing new study shows that benefits of time-restricted feeding on subcutaneous adipose tissue depend on the innervation of subcutaneous white adipose tissue in mice (99). These basic research studies provide a strong rationale for future studies of depot differences of innervation, angiogenesis, and vascularization of these processes in human adipose tissues. Studies that visualize innervation and vascularization using adipo-clearing methods (19) will undoubtedly advance knowledge of this rapidly advancing aspect of adipose tissue biology.

12. ADIPOCYTE SECRETORY PRODUCTS: LIMITED KNOWLEDGE OF DEPOT DIFFERENCES AND RELATIONSHIP TO METABOLIC HEALTH

Adipose tissue secreted factors include 100 adipokines, cytokines, and growth factors. These agonists act at the autocrine and paracrine levels to modulate local and systemic metabolism (23, 67) (**Figure 3**). Tilg et al. (147) and Lumeng and colleagues (63, 110) provide a thorough review of adipokines and immune cells in metabolic inflammation (also known as metainflammation). Adipokine and cytokine levels in adipose tissues vary with circadian rhythms and levels of tissue and systemic inflammation (106, 107). Current knowledge of depot differences in adipokine

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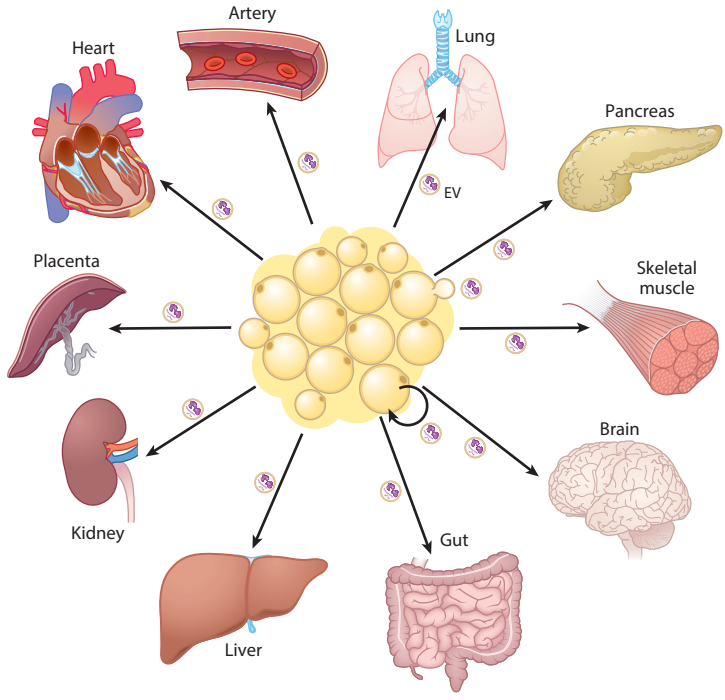

Figure 3

Communication between adipocytes and other organs. New roles for the two main adipokines have been described: Leptin could be a key driver of fibrogenesis in multiple organs (heart, artery, lung, liver, and kidney) and participates in organ failure; adiponectin's new roles include mitochondrial function in the heart, nutrient transport in the placenta, and PPARγ activation in adipocytes. Fatty acid esters of hydroxy fatty acids act on all metabolically important organs and have anti-inflammatory and antidiabetic actions. EVs secreted by adipocytes transport mRNA, miRNA, and protein cargo. They actively participate in the cross talk between adipose tissue and other organs. Abbreviation: EV, extracellular vesicle.

production with these factors, in addition to body shape, within subject variations in fat distribution and metabolic syndrome remains highly limited. Such studies require highly specialized and difficult-to-perform in vivo measurements of arteriovenous differences in adipokine release across fat depots. Future studies are needed to gain a mechanistic understanding of adipose secretory integrated with in vitro measurements of in vitro secretion rates (130).

The term adipokine refers broadly to molecules secreted from adipose tissues. As such, the term includes factors secreted from adipocytes [e.g., adiponectin, leptin, retinol binding protein 4 (RBP4)] as well as other cell types. These include endothelial cells, smooth muscle cells, and pericytes that secrete pro-inflammatory cytokines and chemokines (TNF, interleukins such as IL6, IL8, and CXCL14), as reviewed recently (63). Here, we focus on recent research that highlights the roles of proteins that are synthesized and secreted by the adipocytes themselves. Because most studies of adipokines assess only circulating levels, important questions of depot differences in their production remain unresolved. Few studies directly address these important questions as a function of age, sex, and adiposity. A study in postmenopausal women shows differences in adipokine release from ASAT and FSAT, clearly showing that further studies are warranted (89).

Leptin and adiponectin at the best-studied adipocyte produced secreted adipokines in the context of obesity and insulin resistance. A recent study concluded that leptin, adiponectin, and PAI1 (plasminogen activator inhibitor encoded by *SERPINE1* gene), rather than other adipokines, are

the major drivers of improvements in metabolic health after a substantial weight loss (76). Leptin levels increase in proportion to obesity, whereas adiponectin, an insulin sensitizing adipokine, declines (76). *SERPINE1* (also known as *PAI*) is produced by both adipocytes and macrophages within adipose tissues in proportion to levels of insulin resistance, independent of obesity. Other adipokine mRNA levels studied did not show these associations but cannot be ruled out because they undergo posttranscriptional regulation that leads to protein level and functional changes. A large body of literature indicates that adipokines and cytokines are tightly regulated at both pre- and posttranscriptional levels (86, 119). Most available studies are limited by evidence solely at either mRNA or circulating levels. Future studies that include fat sampling as well as circulating levels are needed to directly address the depot-dependent mechanisms of their production and release. Current knowledge of this topic is scant. Below, we highlight the importance of understanding depot differences in adipose secretory products.

12.1. Leptin

Leptin was the first secreted product of adipocytes identified. Adipose tissue is the nearly sole source of this hormone. Leptin regulates satiety and body weight; it is now recognized as a regulator of multiple aspects of metabolism and immune function, as well as angiogenesis (2, 43), and as a key driver for fibrogenesis in multiple organs (142, 164). Lower levels of leptin are expressed in visceral omental than ASAT (104, 126). Leptin gene expression is reported to be higher in FSAT than ASAT but does not clearly differ between ASAT and GSAT (25, 89). Leptin release from adipose depots is regulated at multiple levels (pre- and posttranscriptional). The relationships of depot differences in leptin expression and secretion at the tissue level have not yet been studied as a function of body shape.

12.2. Adiponectin

Adiponectin is an abundant, insulin-sensitizing, and anti-inflammatory adipocyte hormone. Strong evidence supports the pathophysiologic importance of the lower levels of circulating adiponectin in obesity and cardiometabolic diseases (96). Adiponectin plays a role in atherogenesis via shifts in immune function and FA oxidation (47). Few data are available on the depot-dependent regulation of adiponectin production and secretion. Intriguingly, new research indicates that adiponectin also plays functions intracellularly, where it activates PPARγ and insulin sensitivity (114). Inflammatory signatures of ASAT and FSAT in postmenopausal women with normal weight or obesity provide a strong rationale for further studies of depot differences between these SATs as a function of age, sex, and body shape (89).

12.3. Retinal Binding Protein 4

In 2005, RBP4 was reported by the Barbara Kahn laboratory (158) to be synthesized and secreted by adipocytes. Adipose RBP4 expression is elevated in obesity and insulin-resistant states. Lowering RBP leads to improved adipocyte and systemic insulin sensitivity (158). Studies in humans are limited but indicate higher production in adipose explants from women compared with those of men (77). Studies that compare depot differences in expression and secretion among SATs are needed.

12.4. Serum Amyloid A

Two isoforms, SAA1 and 2, are expressed in human adipose tissue, mainly by adipocytes (160). SAAs associate with HDL in circulation, reducing its anti-inflammatory effects. In chronic

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inflammatory conditions such as obesity and insulin resistance, SAA protein levels in adipose tissues are increased (26). The anti-inflammatory properties HDL are reduced when associated with the ECM component versican at the cell surface of adipocyte (52). Only limited data on depot differences in SAA expression in human adipose are available. Early studies of ASAT versus GSAT SAA secretion (159) support the importance of further studies of this adipokine. Further work that includes assessment roles of adipocyte SAA1 and 2 expressions at mRNA and protein levels and variations in adipose ECM composition on adipose inflammation and metabolism is warranted.

12.5. Potentially Important Roles of Newly Discovered Human Adipocyte Adipokines and Lipokines

Below we highlight evidence for the importance of several adipocyte adipokines.

12.5.1. CXCL14. CXCL14, a CXC motif chemokine ligand, promotes browning of WAT in mice. Its concentrations in human plasma are decreased with metabolic conditions such as obesity, PCOS, and T2D, but data at the tissue level are limited to ASAT (18, 44). Low ASAT CXLCL14 expression levels are correlated with higher inflammation-related genes and lower expression of insulin sensitivity markers (18). The recent single-cell ASAT ATLAS in aging population showed that CXCL14 is also expressed by preadipocytes and is a marker of aging adipose tissue along with senescent marker genes, particularly in individuals with greater abdominal obesity (154). Its expression is highly correlated with fibrosis and excess ECM remodeling. Its specific role in the depot-dependent remodeling of AT during aging and with obesity merits further study.

12.5.2. Isthmin. Isthmin (Ism1), a hormone secreted by adipocytes in mice, was discovered by Svensson and colleagues (66). It improves glucose tolerance and decreases liver steatosis (122, 163). Ism1 also acts on muscle to increase protein synthesis via activation of mTORC. Ism1 also increases protein synthesis by muscle (94). One study found that ISM1 gene expression in humans was higher in ASAT, and its circulating protein levels were associated with fat distribution (20), adding motivation for further studies of depot differences in the expression of this adipokine.

12.5.3. LRG1. The Cohen laboratory (118) identified LRG1 (leucine-rich α-2-glycoprotein 1) as an anti-inflammatory adipokine synthesized and secreted by adipocytes that promotes insulin sensitivity in mice. Based on the mouse results, it is hypothesized to function as a compensatory mechanism that could dampen inflammation by binding to proinflammatory cytochrome c in the circulation (118). In human studies, circulating levels of LRG1 are higher in obesity and diabetes (20, 79). In this situation, they predict arterial stiffness, endothelial function, and peripheral artery disease (118). Further work on this factor in different human adipose tissues and systemic metabolism is clearly warranted.

12.5.4. Fatty acid hydroxy fatty acids. Probably the most important basic research advance in the field of lipokines and human health was the discovery of a novel bioactive lipid class, fatty acid hydroxy fatty acids (FAHFAs), by Kahn (73). FAHFAs act on all metabolically important organs (skeletal muscle, heart, intestine, pancreas) to regulate insulin sensitivity and risk for diabetes metabolism (6). Via their antidiabetic and anti-inflammatory actions, circulating levels of specific FAHFAs (specifically lower levels of PAHSAs and higher PAHOAs) predict risk for developing impaired glucose homeostasis in first degree relatives of type 2 diabetics, independent of BMI and other risk factors (143). As methods for the quantification of specific FAHFAs and other lipid species become more widely available and standardized, it will be important to focus future studies on the potential role of depot differences and body shape in humans.

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In summary, many recent cross-sectional epidemiological and intervention studies of the lipidome and lipid metabolism are becoming available. Future studies that address depot-dependent FA metabolism and their metabolic consequences are needed.

12.5.5. Extracellular vesicles secreted by adipocytes play a central role in organ cross talk: need for future studies of depot differences. Adipose tissues are major contributions to the secretion of EVs that impact systemic metabolism. EVs carry cargo that signal on local (autocrine and paracrine) as well as endocrine (85) levels, as extensively reviewed by Le Lay & Scherer (85). In brief, the highest percentage of EVs in the circulation originates in adipose tissues. They carry proteins, hormones, mRNAs, and miRNAs. Thus, adipose tissues function as an integrator and major driver of whole-body nutrient metabolism. Currently, there is only limited knowledge of their clinical importance, and the majority of the studies have been performed on mice (115, 150, 162) or adipose-derived stem cells (38, 136). Future studies of depot differences in factors carried in EVs and the impact of body fat distribution on EV numbers and cargo will be especially important for understanding how adipose tissues affect metabolic health.

13. FUTURE DIRECTIONS

We have reviewed current knowledge of depot differences in metabolic and secretory function as well as depot differences in adipose tissue growth, remodeling, and expansion. Single-cell and single-nucleus studies highlight distinct and unique cell populations, especially of adipose precursor cell populations. These studies reveal depot differences between ASATs and VATs as well as among ASATs, GSATs, and FSATs that mediate depot differences in growth and metabolism. It will be important to expand research on how fat distribution is regulated at the whole-body level (139), including analysis of arteriovenous differences across adipose depots when feasible (40). On the whole-body level, recent studies leveraged opportunistic availability of whole-body MRI or CT imaging in large numbers of patients to evaluate how adipose distribution predicts metabolic disease such as diabetes (109). Such studies offer opportunities to assess associations among the major larger depots (ASAT, GFSAT, and VAT) as well depot-dependent contributions to fat distribution and metabolic health. Though beyond the scope of this review, we note that smaller depots closely associated with organs including heart, kidney, gastrointestinal tract, and muscles that exert local as well as downstream systemic effects. In summary, with the recent advances in the depot-specific biology of human adipose tissue that we have described, the field is primed for in depth, multilevel, well-powered studies of the influence of fat distribution on metabolic diseases at molecular, physiological, and population levels.

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