thematic review series

Thematic Review Series: Adipose Biology

Determinants of body fat distribution in humans may provide insight about obesity-related health risks

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Abstract **Obesity increases the risks of developing cardiovascular and metabolic diseases and degrades quality of life, ultimately increasing the risk of death. However, not all forms of obesity are equally dangerous: some individuals, despite higher percentages of body fat, are at less risk for certain chronic obesity-related complications. Many open questions remain about why this occurs. Data suggest that the physical location of fat and the overall health of fat dramatically influence disease risk; for example, higher concentrations of visceral relative to subcutaneous adipose tissue are associated with greater metabolic risks. As such, understanding the determinants of the location and health of adipose tissue can provide insight about the pathological consequences of obesity and can begin to outline targets for novel therapeutic approaches to combat the obesity epidemic. Although age and sex hormones clearly play roles in fat distribution and location, much remains unknown about gene regulation at the level of adipose tissue or how genetic variants regulate fat distribution. In this review, we discuss what is known about the determinants of body fat distribution, and we highlight the important roles of sex hormones, aging, and genetic variation in the determination of body fat distribution and its contribution to obesity-related comorbidities.**—Frank, A. P., R. de Souza Santos, B. F. Palmer, and D. J. Clegg. **Determinants of body fat distribution in humans may provide insight about obesity-related health risks.** ***J. Lipid Res.*** **2019.** 60: **1710–1719.**

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Decades of epidemiological research have shown that body fat distribution influences disease risk independently of total body weight or body fat percentage (1, 2). While early investigators regarded adipose as a rather homogenous tissue, contemporary evidence indicates that discrete fat depots function and respond to metabolic challenges (such as increased caloric intake) in different ways, with significant clinical implications (3). For instance, adipose tissue depots differ in terms of susceptibility to vasculature inflammation, endothelial function, and activity of LPL (a critical enzyme mediating fatty acid uptake into adipocytes) (4). There are also depot-specific differences in lipid turnover in obese individuals, which have been linked to obesity-related comorbidities (5). Additionally, there are data to suggest that factors such as adipokines are differentially released from different adipose tissue depots and this too is with metabolic syndrome (MetS) risk (6).

Body adiposity is located mainly either beneath the skin [subcutaneous adipose tissue (SCAT)] or around internal organs [visceral adipose tissue (VAT)], although it can also be found in bone marrow (yellow bone marrow), retro-orbital and periarticular regions, and within tissues such as muscle (intermuscular) (7) and vital organs, often referred as ectopic fat deposition. Predominantly, adipose tissue is accumulated as SCAT (80–90%) (8), and the main depots of SCAT are the abdominal, subscapular (on the upper back), gluteal, and femoral (thigh) areas (8, 9). The importance of this depot distinction is that SCAT depots are located right under the skin and do not communicate with internal organs. Whole-body studies using imaging techniques have revealed that premenopausal women present with more SCAT in the abdominal and gluteofemoral areas than men, especially superficial SCAT, which would be the adipose tissue that is most proximal to the skin (8). Alternatively, VAT is mainly located inside the intraabdominal cavity in close proximity to major organs, including the liver and intestines. One important distinction with this depot is that it drains its constituents (fatty free acids and adipokines) into the portal circulation (10), where they can exert their actions to affect metabolism (7). It is thought that VAT accounts for 6–20% of total body fat, with higher

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Abbreviations: ERα, estrogen receptor α; GRS, genetic risk score; GWAS, genome-wide association study; KS, Klinefelter syndrome; MetS, metabolic syndrome; SCAT, subcutaneous adipose tissue; Sry, sex-determining region Y; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist to hip ratio.

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amounts in males than in females (8). Additionally, there is a small amount of VAT around the heart, known as epicardial fat.

Several studies have reported positive associations of abdominal VAT accumulation, also known as "android" fat distribution, with mortality, CVD, and the MetS risk (11–16). Risks associated with CVD have been particularly well-demonstrated; for example, waist circumference (WC) and waist to hip ratio (WHR), which are commonly used to measure abdominal fat accumulation, were associated with poor cardiac mechanics, including worse global longitudinal and diastolic strain rate (17) as well as left ventricular remodeling and reduced function (18). Abdominal VAT accumulation has also been linked with systemic oxidative stress, another mechanism that may increase CVD risk (19). Even in the nonobese, abdominal fat accumulation is linked with hypertension (20) and predisposes individuals to diseases associated with MetS (21, 22).

WC, WHR, and dual-energy X-ray absorptiometry imaging methods measure the combined volumes of abdominal VAT and SCAT; thus, these measures cannot speak to the relative contributions of abdominal VAT versus SCAT to disease risk. However, the metabolic activity of abdominal SCAT has been associated with a worsening of plasma lipids, insulin, and C-reactive protein, while abdominal VAT is associated with dysregulated glucose homeostasis and fatty liver (23). In the Jackson Heart Study, while both abdominal VAT and SCAT volumes were positively correlated with fasting plasma glucose and triglyceride levels, VAT deposition in the abdomen was most strongly associated with hypertension, type 2 diabetes mellitus (T2DM), and MetS risk (24). These data imply that depot-specific mechanisms contribute to different aspects of cardiometabolic risk. In contrast to abdominal VAT, accumulation of fat in the gluteofemoral SCAT depot produces a "gynoid" body fat pattern, and it has long been believed that deposition of excess adipose tissue in this depot is not associated with MetS risk (25–28). In fact, gluteofemoral SCAT fat accumulation has been shown to be beneficial relative to abdominal VAT accumulation. For example, in cross-sectional studies, Vasan et al. (29) demonstrated a protective effect of gluteofemoral SCAT deposition in terms of T2DM and CVD risks, while Min and Min (30) showed that gluteofemoral SCAT was favorably associated with reductions in triglycerides and increased HDL cholesterol levels. In a 15 year longitudinal study, Tatsukawa et al. (31) determined that gluteofemoral SCAT fat deposition was associated with lower T2DM risk compared with abdominal VAT. Hence, many obesity-associated pathologies are correlated with abdominal VAT versus gluteofemoral SCAT deposition.

SEX HORMONES REGULATE BODY FAT DISTRIBUTION

Body fat distribution in humans is sexually dimorphic, with men and women having differential distribution of adipose tissue. On average, premenopausal women accumulate more SCAT fat in the gluteofemoral depot (32–35), whereas men have more abdominal VAT (36). There is a switch in fat deposition in postmenopausal women, who, similar to men, tend to accumulate more abdominal VAT, even after adjustment for total body fat, age, or both (37). The prevalence of metabolic diseases associated with abdominal obesity, such as insulin resistance and CVD, also increase in postmenopausal women (38, 39). Thus, there is evidence to suggest that sex and sex hormones are key determinants of body fat distribution. In the following sections, we will describe how the sex hormones, estrogen and testosterone, are implicated in body fat distribution.

ESTROGENS AND BODY FAT DISTRIBUTION

In an effort to begin to understand how sex hormones influence body fat distribution, data have been accumulated in both human and rodent studies. In both cases, human and rodent studies demonstrate that estrogens drive fat accumulation in the gluteofemoral SCAT depot rather than in the abdominal VAT depot (40–42), implicating estrogens as determinants of body fat distribution (37, 43, 44). In girls, increases in circulating estrogens occur during puberty onset and coincide with a marked increase in gluteofemoral SCAT fat deposition (45). The resulting "gynoid" fat distribution is typical of reproductive-aged women; however, as ovarian production of estrogens declines after menopause, abdominal VAT mass increases. Estrogen replacement therapy in postmenopausal women decreases abdominal VAT mass (46). Moreover, the ability of estrogens to affect body fat distribution is not confined to women. Evidence of the benefit of estrogens in men and male mice is demonstrated by studies showing that loss of estrogen signaling in males promotes obesity and impairs glucose metabolism (47–50). Additionally, estrogens attenuate the conversion of cortisone to cortisol in adipocyte progenitor cells of male mice, thereby reducing their adipogenic capacity and suppressing fat accrual (51). Also, pharmacological inhibition of circulating estrogens in men is associated with increased fat mass (52, 53). Taken together, these data support that estrogens per se mediate preferential fat accumulation in the SCAT, but the mechanisms remain unclear.

Estrogens are mainly produced by the ovaries in premenopausal women and by the testes in men, but there is also local production of estrogens in adipose tissue mediated by aromatase; thus, estrogens can have a local effect in adipose tissue as well (54, 55). In general, estrogens act through binding of estrogen receptors in a wide variety of organs, including adipose tissue (56, 57). Estrogen receptor α (ERα) has been shown to impact whole-body energy expenditure, body fat accumulation, and glucose homeostasis both in humans and mice (58). Specifically, both male and female mice with total body deletion of ERα (ERαKO mice) are obese, insulin resistant, and dyslipidemic (59); similarly, knockout of ERα selectively in the adipose

tissue of mice increased adipocyte size, adipose tissue inflammation, and fibrosis, and altered fat distribution in both males and females (60, 61).

Importantly, estrogens modulate lipolysis and lipogenesis predominately via ERα, thereby impacting adipose tissue expansion and remodeling. In all mammalian species, energy is stored primarily in white adipose tissue as triglyceride. In face of a prolonged positive energy balance, adipose tissue expands through hyperplasia (an increase of the number of cells through adipogenesis) or hypertrophy (an increase in adipocyte size via lipogenesis) (62). During a "healthy" adipose tissue expansion, when adipose tissue reaches the diffusional limit of oxygen, a stress signal is induced to promote angiogenesis, and remodeling of the extracellular matrix occurs to facilitate further expansion and minimize hypoxia, or lack of oxygen, within the adipose tissue. At the same time, cells from the stromal vascular fraction of adipose tissue, which includes preadipocytes, endothelial cells, immune cells, and fibroblasts, among others (63), also face functional changes in response to alteration in the energy status/stress, and this contributes to adipose tissue expansion and remodeling (64). During chronic overnutrition, however, adipose tissue expands beyond the tissue's ability for adequate angiogenesis and remodeling, which results in hypoxia, fibrosis, and adipocyte death, which are major contributors to metabolic disturbances, as seen in obesity and diseases such as T2DM (65). On the other hand, in situations where metabolic fuels are not sufficient to meet energy needs, a lipolytic cascade is initiated and results in the breakdown of triglycerides into free fatty acids and glycerol. Thus, adipose tissue is expanded and remodeled in response to alterations in the energy status/stress (64).

There are data that peripherally administered estrogens inhibit lipid storage in VAT (66), which is evidenced by the fact that estrogens generally decrease LPL activity (67) and expression of genes associated with lipogenesis in VAT (68). For example, Lundholm et al. (68) reported that estradiol treatment downregulated lipogenic genes in human hepatoma Huh7 cells transfected with ERα. However, the effects of estrogens on LPL seem to be adipose depot specific: in premenopausal women, LPL activity is increased in gluteofemoral SCAT adipocytes compared with abdominal VAT adipocytes (69). Similarly, Lindberg et al. (70) reported that estradiol administration to postmenopausal women stimulated LPL-mediated lipid accumulation in the gluteofemoral SCAT depot. In the study of Cox-York et al. (71), postmenopausal women were treated for 2 weeks with transdermal estrogen replacement therapy, and adipose tissue-derived stem cells were harvested from abdominal or gluteofemoral regions; interestingly, estrogens increased adipogenesis from gluteofemoral but not abdominal adipose tissue-derived stem cells.

Estrogens facilitate lipolysis, as evidenced by studies where estradiol treatment of isolated rat adipocytes increased cAMP levels and lipolysis (72). Also, estrogen replacement of ovariectomized rats increased adenylate cyclase activity (73) and restored lipolysis (74). However, the effects of estrogens on lipolysis in humans are controversial and likely to be adipose tissue depot specific (70, 75). Pedersen et al. (76) showed that estrogen therapy led to lower lipolytic activity in gluteofemoral SCAT (in terms of decreased hormone-sensitive lipase activity), and increased gene expression of α2A adrenergic receptors, which are anti-lipolytic in nature; similar results were observed in excised gluteofemoral SCAT treated with estradiol. Lastly, in an additional study to determine whether ERα is involved with lipolysis, adipocytes isolated from human SCAT were treated with propyl pyrazole triol (a potent ERα agonist) or tetrahydrochrysene (a potent ERα agonist and ERβ blocker); and the data suggest that both pharmacological agents increased α2-AR mRNA expression similarly to estradiol, demonstrating that estrogen's ability to promote gluteofemoral fat deposition may be mediated by ERα (76).

TESTOSTERONE AND BODY FAT DISTRIBUTION

Adult men have lower average body fat percentages compared with adult women. Despite these differences in total body adiposity, in adult men, abdominal VAT depots tend to be larger than in premenopausal women. Studies have sought to determine how testosterone acts to regulate body fat distribution; however, a clear understanding is still lacking. In men, testosterone production increases in puberty (45) and starts to decline after the age of 20–30 years by up to 1% per year, reaching the lowest levels in men 70 years old (77). Decreases in testosterone are associated with increased abdominal VAT accumulation (78, 79), and restoration of physiological levels of testosterone was shown to decrease abdominal VAT (80, 81). There are data that testosterone directly promotes lipid mobilization and inhibits lipid uptake in adipocytes; therefore, loss of testosterone would be expected to increase lipid uptake in adipose tissue. Indeed, treatment with dihydrotestosterone, the major active metabolite of testosterone, suppressed LPL activity and inhibited adipogenesis in adipocyte cultures derived from abdominal VAT and gluteofemoral SCAT depots of both men and women (albeit to a greater extent in men) (80). It is important to state that testosterone regulates adiposity in women as well, as evidenced by studies of women with polycystic ovary syndrome, in which they present elevated levels of testosterone and tend to accumulate more fat in the VAT (82).

Regardless of its direct role in facilitating fat distribution into one depot or the other, testosterone has been shown to enhance the lipolytic capacity of cultured male rat adipose precursor cells by increasing the number of β-adrenergic receptors and the adenylate cyclase activity (83). An increase in fatty acid turnover in conjunction with LPL inhibition has been observed in the adipose tissue of men treated with testosterone (84). Evidence of direct action of testosterone in adipose tissue also comes from studies that have demonstrated the presence of testosterone receptors (85) and testosterone binding (86) in both human and rodent adipocytes. Consistent with these data,

long-term testosterone deficiency has been shown to reduce fat oxidation in men, and testosterone therapy upregulated lipolytic activity from abdominal VAT deposits, but not from gluteofemoral SCAT depots (75). Interestingly, short-term testosterone suppression increased postprandial fatty acid storage in the gluteofemoral SCAT depot (87), as well as LPL activity (88), further implying that physiological testosterone levels inhibit meal-derived fat storage in the gluteofemoral SCAT region, possibly through suppression of LPL activity in the gluteofemoral depot. Because these molecular changes occur prior to changes in regional adiposity, modulation of LPL and meal-derived fatty acid partitioning may contribute to testosterone's ability to direct body fat accrual away from the gluteofemoral depot.

AGING AND BODY FAT DISTRIBUTION

With aging, adipose tissue undergoes critical changes to its abundance, distribution, cellular composition, inflammatory status, cellular senescence, adipose-derived hormone production, and action (89). In regard to body fat distribution with aging, in humans, there is a clear shift from primarily SCAT to VAT fat accrual (89), which is linked to increased risk for obesity and T2DM in older individuals. Aesthetic changes can be observed in association with SCAT loss, such as sunken cheeks, thinning of the skin over the hands and legs, and an increase in wrinkles (89). Also interesting is the fact that macrophages accumulate in the SCAT with aging, but no significant changes are seen in VAT depots, suggesting that the site of adipose tissue inflammation in the elderly is linked with SCAT. Telomere length is also shortened with aging in the stromal vascular fraction of SCAT depots only, which may contribute to the increased senescent cell burden (89). As in humans, rodents face adipose tissue redistribution with aging toward VAT accumulation, which is also associated with age-related diseases, such as insulin resistance, and reduced longevity (90).

Epidemiological data of the National Health and Nutrition Examination Survey from 2011 to 2014, in which supine sagittal abdominal diameter/high and WC/high ratios (both indicators of abdominal VAT accumulation) were measured, show that, while BMI reaches its zenith around 40–49 years of age in men and around 60–69 years of age in women, abdominal VAT increases through age 69 for both sexes (91). Other studies suggest that while women are characterized by higher percentages of body fat through their entire life span when compared with men, these sex differences in the amount of abdominal VAT mass are not consistently seen in older age groups (8). In the STRAMBO study, abdominal VAT was higher in men over 81 years old compared with men in their 20s (92). Alternatively, National Health and Nutrition Examination Survey data show age-related increases in abdominal VAT accumulation in premenopausal women of European and African ancestry (93), indicating that an effect of age to promote abdominal VAT occurs prior to complete loss of ovarian estrogens. These data are consistent with previous reports showing an association of abdominal VAT accumulation with age in premenopausal women (94), as well as age-related increases in abdominal VAT in Hispanic adults (95). Thus, while it is clear that sex hormones mediate some of the effects of aging to promote abdominal VAT accumulation, other factors, such as age per se and total body weight gain, also contribute to age-related adipose tissue redistribution.

GENETIC VARIANTS ASSOCIATED WITH BODY FAT DISTRIBUTION

SNPs

Obesity in humans is genetically regulated and disruption of function of a single gene can result in monogenic obesity. An example of this is the identification of a congenital mutation of the leptin gene in severely obese children (96). Subsequent studies in animal models have delineated the mechanisms underlying this genetic defect, illustrating the important role of leptin signaling to the CNS in regulating energy intake and overall body weight. In addition, molecular genetic studies utilizing families and twins suggest an overall heritability of BMI between 40% and 70% (97). However, evidence generated over the past decade does not indicate that defects in single genes drive obesity in most people. Rather, studies of the association of common genetic variants (known as SNPs) with quantifiable obesity-related traits have shown that the genetic regulation of obesity likely depends on the combination of many SNPs, each contributing a relatively modest effect (98). Such genome-wide association studies (GWASs) have not been restricted to general measures of obesity, such as BMI or overall body fat percentages, and have identified approximately 100 SNPs associated with specific body fat distribution traits (such as WC, WHR, and abdominal VAT volume), some in a sex-specific manner. Of note, unlike forms of monogenic obesity in which the mechanisms of the genetic defect may be well-understood, the mechanisms linking common SNPs (or combinations thereof) identified through GWASs with body fat distribution traits remain largely unknown.

Meta-analyses published by the Genetic Investigation of Anthropometric Traits (GIANT) consortium have identified multiple SNPs associated with WC and WHR, as well as more general measures of overall obesity, such as BMI (99–101). Interestingly, SNPs associated with BMI or body fat amount were located in chromosomal regions enriched for CNS genes, while SNPs associated with body fat distribution were predominately located in proximity to genes involved in peripheral adipose tissue function. These data indicate that the genetic architecture underlying body fat distribution influences mechanisms related to adipose tissue development and metabolism independently of the CNS involvement. Subsequent studies further this notion, showing that genes proximal to many of the loci associated

with body fat distribution traits are directly involved in SCAT regulation and metabolism, including lipolytic and lipogenic pathways (102). In a multi-center study of Spanish adults, de Luis et al. (103) reported an association between WC and the SNP rs6923761, located in proximity to the glucagon-like peptide 1 receptor (*GLP1R*). The authors acknowledge that the mechanistic link between this SNP and WC remains unclear, but suggest that it may affect adipogenesis in the abdominal VAT depot (104). Interestingly, treatment with liraglutide (a *GLP1R* agonist) reduced abdominal VAT to a greater extent than diet alone in obese diabetic patients (105), and SNP carriers had larger decreases in WC and WHR than noncarriers after liraglutide (106). It would be interesting to more precisely determine the mechanistic link; doing so may enable clinicians to predict the efficacy of liraglutide treatment based on genotype. SNPs close to antioxidant genes producing superoxide dismutase and catalase have also been associated with body fat distribution, and obese carriers of two distinct SNPs had more abdominal VAT accumulation compared with obese noncarriers, further supporting a role for genetic regulation of abdominal VAT at the level of the adipose tissue (107). Additionally, four SNPs, rs2070424, rs7880, rs7943316, and rs21001179, were also shown to be associated with greater abdominal VAT volumes (107).

While genetic variations no doubt play a role in obesity and its etiology and sequelae, the effect of genetic variants to be directly related to deposition of adipose tissue is likely additive, with the effect of any one SNP in isolation being modest. Specifically, SNPs associated with body fat distribution have relatively weak single effect sizes (98, 108). Aggregation of multiple SNPs into a composite genetic risk score (GRS) may be a better metric by which to assess the genetic contribution of SNPs to body fat distribution because individuals do not inherit SNPs in isolation, but rather in combinations from their parents (98). Importantly, GRSs have been shown to correlate with certain anthropometric measures of body fat distribution and metabolic health. For example, Fehlert et al. (109) compiled GRSs comprising 65 SNPs reported to have genome-wide significance for body fat distribution, and correlated those scores with MRI from 915 European subjects. The authors reported a significant association between GRS, WHR, and impaired glucose metabolism, and suggest that GRS may be a useful tool to predict future metabolic disease. GRSs have also been associated with an increased abdominal VAT to gluteofemoral SCAT ratio in children (110).

There may be sexual dimorphisms in the manifestations of the SNPs, such as rs2605100 located near the gene, lysophospholipase-like 1 (*LYPLAL1*), which was shown to be significantly associated with WHR in women only (99), and Fox et al. (111) identified an SNP near *THNSL2* (rs1659258) that was significantly associated with abdominal VAT in women only. Subsequent meta-analyses showed that 7 out of 13 (112) and 19 out of 49 SNPs (101) were more strongly associated with WHR adjusted for BMI in women compared to men (101). In 2001, Perusse et al. (113) demonstrated an association between several chromosomal variants and abdominal VAT accrual in the Quebec Family Study cohort. While not a GWAS, these data were interesting because the chromosomal regions were close to genes involved in sex steroid production. Finally, a more recent study linked GRSs for body fat distribution to decreasing serum levels of sex hormone binding globulin (SHBG) (a plasma glycoprotein that binds and solubilizes both estrogens and androgens), further providing data that the genetic architecture driving body fat distribution directs sex hormone function as well (114).

Sex chromosomes

Of particular note, while multiple GWASs have studied sex differences in genetic variation, the contribution of sex chromosomes to determine body fat distribution has largely been ignored. This is due to the historical belief that sex chromosomes contribute little to the genetic regulation of autosomal phenotypes beyond initiating and maintaining sexual differentiation of the gonads. However, human and rodent models suggest that this is not the case. For example, men with Klinefelter syndrome (KS) possess an extra X chromosome (XXY males) and increased measures of abdominal obesity, such as WC. Testosterone production is frequently inhibited in KS patients; therefore, hypogonadism confounds these associations with body fat distribution; however, it is important to note that there is an increased WC observed in prepubertal KS patients (115).

In rodent models, manipulation of gonadal development has led to stronger evidence for sex chromosome effects to alter total body adiposity and body fat distribution. In the four core genotype mouse model, the sex-determining region y gene (*Sry*) is deleted from the Y chromosome and transgenically expressed on an autosome. *Sry* is necessary and sufficient for testes development; thus, transgenic expression of *Sry* in females allows the generation of different combinations of testes and sex chromosomes. In total, the four core genotype model comprises four "sexes": XX mice with either male or female gonads, and XY mice with either male or female gonads. At 75 days of age, gonadal males (of either XX or XY background), on a chow diet, were heavier and presented with a greater body adiposity than gonadal females, implying a role of sexual hormones. At the same time, XX mice were heavier than XY mice, especially XX gonadal female mice, suggesting an effect of sexual chromosomes to determine body adiposity. In order to distinguish between the impact of sexual hormones versus sexual chromosomes to determine body weight and adiposity, mice were then gonadectomized at 75 days of age to remove the acute gonadal hormone action. At 10 months after gonadectomy, XX mice were still heavier and presented with greater body adiposity than XY mice, especially XX gonadal female mice, despite the absence of gonadal secretion. Thus, the authors concluded that male-female differences in the number of X chromosomes influence body weight and adiposity in the opposite direction to the male-female differences in gonadal hormones (116). Additionally, after gonadectomy, XX mice gained more SCAT versus XY mice, suggesting that sex chromosomes

might influence body fat distribution as well, which is consistent with the preferential gluteofemoral SCAT deposition found in women (116). To further confirm the role of the number of X chromosomes to determine body weight and adiposity, in another series of experiments, the same group used XX, XXY, XY, and XO mice, and after gonadectomy, they observed higher body weight and adiposity in mice with two X chromosomes, concluding that the presence of the Y chromosome appeared to have no effect, and the inherent genetic difference conferred by the presence of two X chromosomes might be determinant for body weight and adiposity (116). The mechanistic link with this phenomenon appears to be related to the genes escaping X inactivation in XX models.

Epigenetic effects

Epigenetic mechanisms, whereby changes in gene expression are not due to polymorphisms in DNA sequence, but rather to changes in the physical accessibility of DNA regions to intracellular transcriptional machinery, may also contribute to body fat distribution. Benton et al. (117) reported that weight loss significantly decreased DNA methylation in large genomic regions of SCAT depots, and higher DNA methylation was observed in the fat cell DNA methylome of SCAT depots from obese women compared with women who had lost weight. However, Mendelian randomization analyses indicated that obesity drives methylation in 187 BMI-associated CpG loci (regions of genomic DNA where methylation of the cytosine nucleotide can occur) and not vice versa (118). This indicates that higher DNA methylation is secondary to obesity (119). Nonetheless, cross-sectional evidence does suggest that DNA methylation and measures of body fat distribution are associated. For example, 99 protein coding candidate genes in 69 genetic loci were associated with body fat distribution (101). Of these, 22 genes displayed both methylation and altered expression in obese women. Importantly, DNA methylation is a tissue-specific phenomenon; therefore, studies of adipose tissue DNA methylation (as opposed to methylation patterns of peripheral white blood cells, which are more common in the literature) are critical to determining how epigenetic modifications mechanistically affect body fat distribution. Indeed, Agha et al. (120) showed that, while DNA methylation profiles in peripheral blood cells were not associated with adiposity measures, DNA methylation profiles from actual adipose tissues were associated with VAT and the ratio of upper body to lower body fat mass.

Additionally, a recent large meta-analysis of DNA methylation levels of peripheral blood leukocytes did identify 33 out of 40 CpG loci that were significantly associated with body fat distribution traits; however, only methylation of the cg06500161 locus (proximal to *ABCG1*) was associated with all body fat distribution traits (121). Authors noted that the strength of these associations was greater in women versus men (for example, for cg06500161, $P = 1.10 \times 10^{-16}$ for women vs. $P = 1.68 \times 10^{-5}$ for men) (121). This suggests that sexually dimorphic effects of DNA methylation may exist.

A comprehensive characterization of how genetic architecture affects body fat distribution mechanistically does not exist. Development of a truly comprehensive model is complicated by the fact that all variants therefore discovered likely account for only a small fraction of the total heritability of body fat distribution traits. This would seem to suggest that identification and manipulation of any one possible gene variant would have little effect on body fat distribution; however, there are some studies that have shown that manipulation of genes with modest individual effect sizes can still produce clinically beneficial effects for complex diseases and traits. Thus, continued study of how genetic and epigenetic variation impacts body fat distribution through differential regulation of genes is a valuable future endeavor.

DEVELOPMENTAL DIFFERENCES AMONG ADIPOSE TISSUE DEPOTS

Adipose tissue is generally reported as having a mesodermal origin, which comprises axial, intermediate, lateral plate, and paraxial mesoderm (7). These regions are presumed to give rise to local adipose tissue and, as such, to differential expression of genes involved in the development and patterning between different adipose tissue depots. Embryonic stem cells are controlled by several developmental signaling systems in order to differentiate into mesenchymal/mesodermal stem cells, such as Nodal, Hedgehog, wingless (WNT), bone morphogenic proteins, fibroblast growth factors, and developmental/patterning signals, among others. Interestingly, mesenchymal/mesodermal stem cells appear to differentiate to a common white preadipocyte, which subsequently develops into subcutaneous preadipocytes or visceral preadipocytes, which in turn will differentiate into SCAT or VAT (7). However, this pathway remains unclear in the literature, as do the mechanisms that drive the differentiation of a committed white preadipocyte into a subcutaneous preadipocyte or a visceral preadipocyte. Besides mesenteric origin, other potential sources of preadipocytes should be considered, including neural crest, pericytes associated with the blood vasculature, and hematopoietic cells originating from myeloid progenitors (122).

Evidence also suggests that various white adipocytes (from SCAT or VAT) are derived from different precursors. First, adipocytes from different depots have significant differences in the expression of genes, which causes them to be associated to a greater or lesser extent in the development of metabolic disorders (123). In humans and rodents, adipocytes from VAT have higher expression of *HoxA5*, *HoxA4*, *HoxC8*, *Gpc4*, and *Nc2f1*, which are transcriptional regulators involved in early embryonic development, body patterning, and cell specification; while adipocytes from SCAT have higher expression of *HoxA10*, *HoxC9*, *Twist 1*, *Tbx15*, *Shox2*, *En1*, and *Sfpr2*, among others (122, 123). These data are also supported by GWASs that suggest that body fat distribution is associated with variations in genes involved in pattern formation during embryonic development (124). Other evidence includes the variations in

chronology of their appearance: In rodents, white adipocytes develop after birth; first, SCAT depots and later, VAT depots. In humans, white adipocytes develop during the second trimester and, by birth, both SCAT and VAT are well developed (7).

CONCLUSIONS

Where body fat is distributed is clinically important. Higher VAT mass relative to subcutaneous fat is associated with a worse metabolic risk, making understanding the determinants of body fat distribution imperative. Sex hormones, particularly estrogens and testosterone, drive body fat accrual in a depot-specific manner, through depot-specific mechanisms such as lipolysis. VAT tends to increase with age in humans; while aspects of this phenomenon depend on sex hormone status, other factors, such as total body fat accumulation, also have roles in determining body fat distribution. The genetic contribution to body fat distribution is becoming increasingly clear and likely involves gene regulation at the level of the adipose tissue itself. However, much remains unknown regarding the many ways in which genetic variants mechanistically regulate fat distribution. Recent epidemiological data show that obesity rates in the adult US population have not abated. Given the highly obesogenic environment of the United States and developed world, reducing overall body weights across the population will be exceedingly difficult. Better understanding of the mechanisms underlying body fat distribution will allow the development of therapies that target body fat distribution with the aim of predisposing weight gain away from metabolically dangerous body fat depots, thereby reducing chronic disease risk and obesity-related comorbidities.

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