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Adipose Tissue Heterogeneity: Implication of depot differences in adipose tissue for Obesity Complications

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Abstract

Obesity, defined as excess fat mass, increases risks for multiple metabolic diseases, such as type 2 diabetes, cardiovascular disease and several types of cancer. Over and above fat mass *per se*, the pattern of fat distribution, android or truncal as compared to gynoid or peripheral, has a profound influence on systemic metabolism and hence risk for metabolic diseases. Increases in upper body adipose tissue (visceral and abdominal subcutaneous) confer an independent risk, while the quantity of gluteofemoral adipose tissue is protective. Variations in the capacity of different depots to store and release fatty acids and to produce adipokines are important determinants of fat distribution and its metabolic consequences. Depot differences in cellular composition and physiology, including innervation and blood flow, likely influence their phenotypic properties. A number of lines of evidence also support the idea that adipocytes from different anatomical depots are intrinsically different as a result of genetic or developmental events. In this chapter, we will review the phenotypic characteristics of different adipose depots and mechanisms that link their depot-specific biology to metabolic complications in men and women.

1. Adipose tissue anatomy and distribution

1.1 Adipose tissues are present in discrete depots throughout the body

The adipose organ includes numerous discrete anatomical depots (Shen et al. 2003) (Figure 1). The size of fat stores is highly variable, ranging from 5 to 60% of total body weight. Subcutaneous adipose tissues (SAT) store >80% of total body fat in the body. The most commonly defined and studied subcutaneous (sc) depots are the abdominal, gluteal and femoral. A layer of connective tissue (Scarpa's fascia), visible on computerized tomography (CT) separates deep from superficial sc fat. These sc layers are functionally distinct and independently correlate with metabolic complications of obesity (Smith et al. 2001).

Intraabdominal fat depots are associated with internal organs. In humans, intra- and retro-peritoneal depots represent 10~20% of total body fat in men and 5~10% in women. Intraperitoneal or so-called visceral adipose tissues (VAT) are associated with digestive organs, and include the omental (hangs off the stomach), the mesenteric (associated with the intestine), and epiploic (along the colon).

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There are also numerous smaller adipose depots such as epicardial and intermuscular that may serve specialized functions related to their neighboring tissues (Sacks and Fain, 2007;Cinti, 2001). Recent literature (re)discovered the presence of brown adipose tissues (BAT) in adult humans. BAT is found in cervical-supraclavicular, perirenal, and paravertebral regions. Unlike white adipocytes which have mesenchymal or pericyte origins (Tang et al. 2008), brown adipocytes are derived either from myogenic lineage or trans-differentiation from white adipocytes ("brite") (Kajimura et al. 2010). While BAT plays critical role in cold-induced thermogenesis, its potential in the control of adaptive thermogenesis, body weight and metabolic disorders in humans has not been yet proven (Ravussin and Galgani, 2011).

1.2 Cellular composition of adipose tissues

White adipocytes are characterized by a unique morphology with unilocular lipid droplets that occupy 95% of the cell volume and thereby determine the cell size, which ranges from ~20 to 200 micrometers. Other cell types are also present within ATs. These stromal vascular cells (SVC), usually isolated after collagenase digestion, include preadipocytes, endothelial cells, pericytes, as well as various immune cells (macrophages, T-cells, neutrophils, lymphocytes). Multipotent stem cells are also present and due to easy access, the potential of AT in regenerative medicine has been proposed. Although other cells outnumber adipocytes in the tissue (1–2 million adipocytes and 4–6 million other cells are present in a gram of human AT), adipocytes constitute ~90% of the tissue volume. VAT includes an abundance of milky spots and lymph nodes where lymphocytes accumulate (Gabrielsson et al. 2003;Litbarg et al. 2007). Thus, Pond hypothesized that VAT plays a special role in immunity, potentially explaining the growth of VAT in response to infections such as HIV (Pond ,2005). Visceral as well as epicardial AT also include mesothelial cells (Darimont et al. 2007;Sacks and Fain, 2007). Undoubtedly, depot-differences in cell populations contribute to depot-differences in adipokine production, and can contribute to variations in adipocyte function via paracrine interactions.

2. Determinants of fatness and fat distribution

Race, sex and age affect AT distribution. However, the mechanisms involved are barely understood.

2.1 Sex differences

Women generally have higher adiposity than men. In addition, men accumulate more fat in central area (both VAT and abdominal sc), while women accumulate more in lower body sc (gluteofemoral) (Geer and Shen, 2009). Factors that govern this sexual dimorphism are not clear. Much attention has been paid to the role of sex steroid hormones (estrogen and androgen), but mechanisms for depot-specific effects remain poorly understood. Women with polycystic ovary syndrome, characterized by a hyperandrogenic state, are prone to central obesity (Escobar-Morreale and San Millan, 2007) whereas testosterone-treated men have less fat mass with selective loss of central fat (Allan and McLachlan, 2010). The mechanisms through sex steroids regulate AT are poorly understood.

2.2 Racial differences

Caucasians exhibit lower rates of obesity compared to minority groups. African Americans and Hispanics have relatively less visceral fat than the whites (Carroll et al. 2008;Katzmarzyk et al. 2010). A recent study showed that South Asians have more central adiposity compared to Caucasians (Anand et al. 2011). Genetics as well as interplay with environmental factors likely play a role in determining ethnic differences in fat distribution.

2.3 Age

With aging, fat accumulates in central area, both visceral and abdominal sc (Kuk et al. 2009). While substantial evidence exists that obesity increases risk for morbidity and mortality in young people, its effect in the elderly is much more complex (Chapman, 2010).

3. Morphological and functional heterogeneity among adipose depots

Regional differences exist in AT morphological characteristics and function. Depots differ in cellular composition, microvasculature, innervation, metabolic characteristics, extracellular matrix composition, and secretory products. Although we will discuss each of these characteristics individually, it is important to note that they collectively comprise the "microenvironment" within each depot that contributes to depot differences in metabolism and endocrine function.

3.1 Depot differences in morphology and cellularity

Generally, adipocytes are smaller in visceral than sc in women, while they are similar in size in men and extremely obese women. The number of stromal cells (nonadipocytes) per gram of AT is greater in omental than abdominal sc (van, V et al. 2004;Shahparaki et al. 2002). Differences in preadipocyte populations have also been reported. SAT contains higher numbers of preadipocytes (Tchkonia et al. 2005).

3.2 Depot differences in adipocyte metabolism

White ATs store more than 95% of total lipid as neutral lipids, triglyceride (TG), and release them as FFA and glycerol in highly regulated fashions involving multiple hormones, enzymes and proteins.

3.2.1 Lipolysis

3.2.1.1 Cellular mechanisms: Lipolysis is defined as hydrolysis of TG into FFA and glycerol. Adipose TG lipase (ATGL) hydrolyzes TG into diacylglyceride, which is further broken down to FFA and glycerol by hormone sensitive lipase (HSL, respond to beta-adrenergic stimuli) and monoacylglyceride lipase. Once released from adipocytes, FFA bound to albumin in the circulation are delivered to muscle (oxidation), liver (TG synthesis or oxidation), and adipocytes (reesterification). Glycerol is delivered to the liver and used for hepatic glucose production, as the adipocyte normally lacks glycerol kinase.

Recent studies point to the importance of lipid droplet associated proteins and lipases in the dysregulation of adipocyte lipolysis in obesity, but their roles in depot-differences in adipocyte metabolism are not yet clear. HSL and perilipin (a lipid droplet protein that regulates both basal and stimulated lipolysis), are known to be differentially expressed between omental and sc, potentially contributing to depot differences in lipolysis (Arner, 1995;Wang et al. 2003).

3.2.1.2 In vitro studies: Omental adipocytes exhibit similar or lower basal (spontaneous) lipolysis but higher responses to adrenergic agonists (fold over basal) (Fried et al. 1993;Rebuffe-Scrive et al. 1990;Tchernof et al. 2006;Boivin et al. 2007). Expression levels of antilipolytic alpha 2 adrenergic receptors (AR) are lower while lipolytic beta-AR are higher in omental, contributing to the higher responses to adrenergic stimuli in this depot (Leibel et al. 1989a;Lonnqvist et al. 1997). Omental adipocytes are also reported to be less sensitive to the antilipolytic effects of insulin *in vivo* (Meek et al. 1999). Thus, in some situations, i.e, stress or the postprandial state, the contribution of VAT-derived FFA may become more significant, up to 40% (Meek et al. 1999).

With regard to heterogeneity in lipolysis between sc depots (femoral, gluteal and abdominal), most studies indicate that upper body adipocytes are more responsive to beta-adrenergic agonists, and lower body adipocytes are more responsive to the antilipolytic effects of alpha 2 adrenergic agonists with lower lipolytic responses to mixed agonists (Leibel et al. 1989b). Data on the antilipolytic effect of insulin among different sc depots are inconclusive (Johnson et al. 2001;Fried et al. 2010).

3.2.1.3 In vivo analysis: Jensen's group evaluated the relative contributions of viscerally derived FFA to the portal and systemic circulation in humans (Nielsen et al. 2004). FFA release from visceral to portal vein increases with increasing mass of visceral fat, although its relative contribution is highly variable at a given visceral adiposity (5 to 50%). Thus, VAT-derived FFA in some obese can affect hepatic function. However, the splanchnic FFA to systemic FFA was 6% (lean) to 13% (obese), suggesting VAT-derived FFA is not a significant contributor of FFA delivery to the periphery i.e. skeletal muscle. Jensen's group found that *in vivo* lipolytic activity is greater in upper body than lower body sc in both sexes, and that upper body sc accounts for ~70% of systemic FFA rate of appearance (Meek et al. 1999;Jensen, 1995).

Few studies have addressed *in vivo* factors that could affect adipocyte lipolytic activity. In rodents, there are depot differences in innervation, but this possibility has not been documented in humans. Differential sympathetic innervation of VAT may also mediate the preferential mobilization of these depots under hypocaloric conditions (Bartness and Song, 2007). The rate of removal of lipolytic products can also affect the rates of lipolysis *in vivo*. Blood flow per kg of fat tended to be higher in omental than abdominal sc or perirenal depots in humans, but differences were not statistically significant with a relatively small sample size (Virtanen et al. 2002). In rats, blood flow is ~5-fold greater in mesentery than other depots (Crandall et al. 1984;West et al. 1989). These physiologic factors merit further study as determinants of adipocyte function.

3.2.2 TG synthesis and storage

3.2.2.1 Cellular mechanisms: In adipocytes, TG is synthesized from FFA esterified to a glyceride-glycerol backbone. The majority of FFAs are delivered through lipoprotein lipase (LPL) breakdown of circulating TG (chylomicron or VLDL), but the direct uptake of circulating FFA also contribute. LPL activity per adipocyte is lower in omental than abdominal sc in women whereas there is no depot-difference in severely obese men (Fried and Kral, 1987;Boivin et al. 2007). In non-obese or moderately obese men, omental fat cell size and LPL activity is higher, particularly at an intermediate waist circumference. Higher LPL activity may favor the preferential fat deposition in visceral depots in men (Boivin et al. 2007). De novo synthesis of FA from glucose or other precursors in human adipocytes is quite low under most circumstances (except refeeding after fasting or a period of undernutrition), as most people consume relatively high fat diets that suppress this process.

The glyceride-glycerol backbone of TG is usually derived from glucose. The rate of glucose uptake into adipocytes is therefore an important determinant of TG storage. Glucose is transported into adipocytes through glucose transporters (GLUT). Adipocytes contain GLUT4, which in response to insulin, localize to the cell membrane, increasing glucose uptake. We demonstrated that glucose uptake and conversion to TG are similar among omental, mesenteric and abdominal sc ATs of men, but uptake per adipocyte is lower in omental of women (which has smaller adipocytes) (Edens et al. 1993). Others demonstrated that omentum is not resistant to insulin-stimulated glucose uptake both *in vivo* (Virtanen et al. 2002) and *in vitro* (Bashan et al. 2007). In fact, glucose uptake (expressed per kilogram AT) was greater in visceral compared to sc (Marin et al. 1987;Virtanen et al. 2002). Blood

flow and GLUT4 protein are higher in omentum, which may increase glucose uptake into the depot, as demonstrated with tracer studies *in vivo* (Virtanen et al. 2002;Veilleux et al. 2009).

Lactate may also be an important source of glyceride-glycerol, via the glyceroneogenic pathway (Hanson and Reshef, 2003). The relative importance of lactate and glucose in regulating TG synthesis among human ATs in different nutritional or physiologic conditions is not known.

3.2.2.2 In vivo analysis of TG and FFA uptake: *In vivo* studies of meal FA uptake or FFA uptake provide definitive evidence for heterogeneity in the metabolism of VAT and SAT. Expressed relative to the same mass AT, meal FA uptake is greater in intraabdominal than abdominal sc in both sexes (Marin et al. 1996;Jensen et al. 2003). The direct uptake of plasma FFA (labeled FA delivered intravenously) is also greater (per unit mass) in omental compared to abdominal sc of women (Koutsari et al. 2011), so this mechanism may contribute to the preferential accumulation of VAT. However, except perhaps in extreme upper body fat distributions, adipocyte size is smaller (women) or similar (men) in omental and abdominal sc. Thus, on a per cell basis, uptake and esterification may be similar or even lower in visceral adipocytes because there are more adipocytes per gram. Alternatively, *in vivo* rates of FA esterification must be balanced with rates of FA mobilization (lipolysis) to maintain smaller/similar fat cell size.

There is also heterogeneity in FA handling in sc depots *in vivo*. Meal FA uptake is greater in upper body than lower body SAT in both sexes (Marin et al. 1995;Romanski et al. 2000), implying the differential meal fat storage does not explain sex-dependent body fat distribution. Jensen's group showed that femoral AT is more efficient in taking up FFAs from the circulation, in proportion to the size of this depot, and proposed that direct FA uptake rather than meal fat uptake or lipolytic rates may explain sex-dependant body fat distribution (Shadid et al. 2007;Koutsari et al. 2011).

Testosterone (T) influences meal fat uptake in men. T administration decreases meal fat incorporation into TG in VAT (omental and retroperitoneal) preferentially (Marin et al. 1996), and into abdominal sc without affecting femoral sc uptake (Marin et al. 1995). These studies provide evidence that T directs TG storage to peripheral rather than central area in men, and may explain the development of central adiposity with declining T with aging (Rebuffe-Scrive et al. 1991). How T affects regional utilization of FA and whether estrogen plays a role in meal fat or direct FFA uptake are not known.

3.3 Depot differences in adipokine production

AT secretes numerous peptide hormones and bioactive molecules that act in auto-, para- and endo-crine fashions to regulate AT and systemic metabolism. Adipocytes produce several hormones, most notably leptin and adiponectin, which modulate appetite, fuel metabolism, innate immune function, and reproduction (Trujillo and Scherer, 2006). Adipocytes also secrete complement factors and acute phase response proteins including serum amyloid A (SAA) (Yang et al. 2006a) and retinol binding protein 4 (RBP4) (Yang et al. 2005), which can influence systemic inflammation and insulin resistance. Other cells within AT produce additional factors, including omentin, visfatin, resistin, TNF-α, IL-6, and IL-8.

Generally the expression of proinflammatory cytokines (IL-6, IL-8, MCP-1, RANTES, MIP-1α, PAI-1) is higher in VAT while leptin and IP-10 expression is higher in SAT (reviewed in (Lee and Fried, 2010)). In addition, molecules involved in innate immunity and the acute phase response and complement factors are overexpressed in VAT. The depot-differences in TNF-α and adiponectin expression levels are inconsistent. Among adipokines,

there is a net release (arterio-venous difference) in IL-6, angiotensin II, and RANTES, but not TNF-α (Madani et al. 2009;Mohamed-Ali et al. 1997;Harte et al. 2005).

Omentin, also known as intelectin and the lactoferrin receptor, is a truly visceral-specific adipokine that is synthesized and secreted from omentum, but not sc (Yang et al. 2006b). Omentin is expressed in non-adipose cells, but the cell type is not yet identified. Omentin levels are decreased in proportion to obesity and level of insulin resistance (de Souza Batista et al. 2007). *In vitro*, omentin increases insulin sensitivity of glucose uptake in human adipocytes (Yang et al. 2006b), suggesting that omentin might 'protect' this depot from the insulin resistance expected from high levels of inflammatory cytokines that are detected. Visfatin was identified as a visceral specific adipokine, but in humans its expression levels are similar between VAT and SAT (Varma et al. 2007).

AT has also been identified as a site of expression of the inflammatory marker C-reactive protein (CRP), resistin (expressed in monocytes in humans) and thrombospondin-1 (reviewed in (Trujillo and Scherer, 2006)) but their functional importance and depot-differences in their expression levels are as yet unclear.

4. Adipose tissue dysfunction in obesity

With the development of obesity, AT becomes increasingly dysfunctional. Both elevated FFA and altered adipokine production in obesity play critical roles in the etiology of obesity-related metabolic complications. FFA increase pancreatic insulin secretion, decrease insulin sensitivity in muscle and liver, increase hepatic VLDL secretion, and induce endothelial dysfunction. Heightened lipolysis from VAT is thought to contribute to visceral obesity related metabolic complications, by increasing FFA delivery directly to the liver.

AT production of proinflammatory cytokines is increased in obesity, contributing to the systemic inflammation that coincides with obesity. As adipocyte become hypertrophic, macrophages infiltrate the tissue, become activated and secrete proinflammatory molecules (FFA, IL-6, SAA), while adipocyte production of antiinflammatory adipokines such as adiponectin is suppressed. Unless the vasculature expands in proportion to the expansion of adipocyte volume, microhypoxia results and contributes to the inflammation within the tissue (Pasarica et al. 2009). The balance of these factors, acting on target tissues especially muscle and liver, influences insulin action, substrate utilization, and inflammation, playing a major role in increasing metabolic risk for type 2 diabetes and cardiovascular diseases (Figure 2).

5. Central obesity is more tightly associated with metabolic complications

Central obesity, particularly visceral obesity, but also including fat accumulation in abdominal sc (apple-shaped, android), confers increased risk for metabolic complications of obesity, whereas lower or peripheral obesity, preferential fat accumulation in gluteofemoral region and leg (pear-shaped, gynoid), is associated with lower risk and may be protective (St-Pierre et al. 2007;Vega et al. 2006;Snijder et al. 2005;Fox et al. 2007;Azuma et al. 2007). Thus, measuring waist and hip circumferences and calculating waist-to-hip ratio (WHR) better identifies abdominally obese subjects at risk of developing metabolic diseases. Clinically, cutoffs of waist circumferences greater than 102 cm in men and 88 cm in women, and WHR greater than 1.0 in men and 0.8 in women are suggested to define those at increased risk (Alberti et al. 2009). Studies using CT or MRI images taken at L2–3 and/or L4–5 to distinguish visceral and abdominal sc depots point to strong independent negative effects of visceral fat mass that are independent of total body fat on metabolic risks (Despres and Lemieux, 2006). Sex differences in metabolic risk are at least partially due to the higher visceral fat mass in men (Despres and Lemieux, 2006).

5.1 Mechanisms linking fat distribution to metabolic complications

5.1.1 FFA—Although depot differences in adipocyte metabolism and endocrine function are clearly important in etiology of obesity related diseases, the relative contribution of VAT compared to abdominal sc is still controversial. The portal hypothesis, originally proposed by Bjorntorp (Bjorntorp, 1990) posits that because VAT drains directly to the liver through the portal circulation and hepatocytes are exposed to high levels of FFA from lipolytically active VAT. FFA can induce hepatic insulin resistance, increasing hepatic glucose production and hence fasting hyperglycemia. In addition, FFA impair the ability of hepatocytes to degrade insulin, resulting in hyperinsulinemia and provide substrate for TG synthesis, contributing to hyperlipidemia via increased VLDL production and hepatic steatosis and nonalcoholic fatty liver disease (Hijona et al. 2010). However, measurements of portal FA in humans do not consistently show higher values in portal than peripheral blood. In obese dogs, however, which have substantial VAT, portal FA levels are clearly elevated, especially during the night (Kim et al. 2007).

5.1.2 Adipokines and cytokines—VAT production of proinflammatory cytokines is higher and this may also contribute to hepatic pathology in obesity (Lee and Fried, 2010). Higher IL-6 and lower leptin levels in portal vein compared to peripheral artery have been reported *in vivo* (Fontana et al. 2007). Cytokines can alter hepatic function, insulin sensitivity and cytokine production. Accordingly, a tight association between portal IL-6 and CRP has been demonstrated (Fontana et al. 2007).

5.1.3 Ectopic fat deposition—Other researchers propose that the level of visceral adiposity is simply a marker for insulin resistance that mainly results from ectopic fat deposition in other tissues, which cause insulin resistance as a result of lipotoxicity. The ‘spillover hypothesis’ suggests that when the SAT reaches its limit for expansion (maximum hypertrophy of existing adipocytes and failure to recruit new adipocytes), excess energy is stored in VAT, then in other tissues including liver, skeletal muscle, and pancreatic beta cells (Danforth E Jr, 2000). Similarly, lipodystrophy, loss of the ability to store excess lipids in AT, can lead to the overdevelopment of ectopic fat stores and hence metabolic perturbations. Given evidence for heterogeneity in the metabolic consequences of obesity for liver and muscle metabolism, it seems likely that both direct effects of an expanded VAT and indirect mechanisms of AT storage capacity that result in ectopic fat contribute to tissue-specific metabolic impairments, within an individual.

5.2 Lessons learned from studies of lipectomy and fat transplantation studies

The removal of intraabdominal fat improves while removal of sc does not affect insulin sensitivity in rodents (Barzilai et al. 1999;Shi et al. 2007). The beneficial effects of AT removal on metabolic risks in human are controversial. Several studies using omentectomy in addition to Roux-en-Y gastric bypass resulted in controversial findings. While one study found beneficial outcome (Thorne et al. 2002), the other two (Csendes et al. 2009;Herrera et al. 2010) did not find additional benefits although the results are somewhat confounded by weight loss due to gastric bypass. In addition, removal of rather large quantity of abdominal sc through liposuction has been shown to be ineffective (Klein et al. 2004). In contrast, weight loss through diet, exercise, or in combination has been proven to be effective in improving metabolic diseases. Diet and exercise cause preferential fat loss from intraabdominal fat than the sc (Chaston and Dixon, 2008).

To test whether there are any intrinsic properties of different depots that contribute to their metabolic effects, fat transplantation has been used by several groups (Tran et al. 2007;Hocking et al. 2008;Foster et al. 2011). Transplantation of inguinal sc to the visceral cavity leads to lower body weight gain with improvement in glucose metabolism in mouse.

While these studies suggest that SAT is intrinsically different from VAT, location also seems to be important as sc to visceral transplants are more beneficial than sc to sc transplantation. Sex-specific properties of adipocyte precursors have also been demonstrated in transplantation studies (Guo et al. 2004).

6. Depot-differences in adipose tissue growth and remodeling

Given the association of excess intraabdominal fat and metabolic disorders, it is important to understand how the growth and turnover of intraabdominal vs. sc adipocytes is regulated.

6.1 Preadipocyte recruitment and adipocyte differentiation

Accumulation of AT depends in part on new adipocyte formation (recruitment of progenitors/preadipocytes and their differentiation into adipocytes), as well as hypertrophy of existing adipocytes. VAT contains fewer adipogenic precursors and they exhibit lower proliferation and differentiation capacity (Hauner et al. 1988;Tchkonia et al. 2006). No depot difference in preadipocyte differentiation however, has been also noted (van, V et al. 2004;Shahparaki et al. 2002). As *in vitro* culture conditions affect cell proliferation and differentiation, it is difficult to extrapolate these *in vitro* findings to the actual adipose biology *in vivo*. Differences in innervation, vascularity, and overall cellular composition of each depot are also undoubtedly relevant *in vivo*. The greater capacity of sc compared to visceral preadipocytes to proliferate may underlie the greater growth of this tissue in response to overnutrition or treatment with PPARγ agonists used for diabetes therapy.

In response to high fat diet, the growth of ATs occurs by a combination of hypertrophy and hyperplasia. In rodents, the capacity of preadipocyte proliferation and recruitment is lower in epididymal than sc depots (Faust et al. 1978). The limited capacity for hyperplasia in intraabdominal depots may contribute to the excessive hypertrophy and thus stress on the existing adipocytes. Accordingly, in obese mouse models, the epididymal fat exhibits much greater rates of adipocyte death/tissue remodeling as reflected in an increased number of macrophages forming crown like structures (CLS) around dead adipocytes (Strissel et al. 2007;Nishimura et al. 2008). CLS are also more numerous in visceral than sc in human (Cinti et al. 2005;Cancello et al. 2006;Harman-Boehm et al. 2007). The numbers of CLS in omentum correlate with the severity of hepatic fibroinflammatory lesions (Cancello et al. 2006) and liver fat content (Kolak et al. 2007), as well as insulin sensitivity (Apovian et al. 2008). Several cytokines, MCP-1, GM-CSF1 and SAA, have been implicated in macrophage chemotaxis and activation (Weisberg et al. 2006;Han et al. 2007). These are expressed at higher levels in omentum (Bruun et al. 2005;Sjoholm et al. 2005), potentially contributing to the preferential macrophage infiltration into the depot. It is noteworthy however, that the number of CLS in human AT even in the obese is much lower than that observed in epididymal fat of rodents.

In vitro, femoral compared to abdominal sc preadipocytes exhibit a lower differentiation capacity (Hauner and Entenmann, 1991;Tchoukalova et al. 2010a). These regional differences may affect the capacity of adipose depots to form new fat cells. Tchoukalova reported that with 8-week overfeeding, upper body sc expands through hypertrophy while lower body sc expands through hyperplasia, suggesting intrinsic differences in expansion capacity between the two sc depots in humans (Tchoukalova et al. 2010b).

6.2 Adipocyte death

There are measurable rates of adipocyte death, although the rates are estimated to be similar in lean and obese (10 years) (Spalding et al. 2008). Human preadipocytes from VAT are more susceptible to apoptotic stimuli (Niesler et al. 1998;Tchkonia et al. 2006), suggesting that there are intrinsic differences in apoptosis between preadipocytes from the two depots.

Preadipocytes from lower body and upper body sc adipose depots respond similarly to TNF-α induced apoptosis (Tchoukalova et al. 2010b).

7. Developmental roots of adipose tissue heterogeneity

Studies using global gene expression analysis reported a depot-difference (VAT vs. SAT) in the expression of developmental genes such as cell differentiation, organogenesis, antero-posterior or dorso-ventral patterning in both mouse and human (Vohl et al. 2004;Gesta et al. 2006;Tchkonia et al. 2007). The differences in gene expression pattern persist even after *in vitro* differentiation of preadipocytes, suggesting the differences are independent of extrinsic factors and different adipocyte progenitors are programmed through epigenetic modulation during early in the development. These studies also suggest that different adipocyte precursors are responsible for a specific adipose depot development and may participate in determining functional differences observed between VAT and SAT. In a recent study in collaboration with Dr. Smith, we found depot differences in developmental gene expression patterns between the two major sc depots, abdominal vs. gluteal (Smith SR and Fried SK, unpublished observation).

8. Conclusions

Unlike other organs, adipose tissues appear in multiple locations throughout the body, both in intraabdominal and sc areas. The distribution of AT has clinical importance, as central adiposity, especially visceral obesity, is more deleterious while lower body fat accumulation may be actually protective. The mechanisms underlying the regulation of regional adiposity and the disproportionate effects of enlargements in visceral fat depots on health of men and women remain enigmatic. Many studies have described depot differences in physiology (blood flow and innervation), cellular compositions, and AT metabolic and endocrine functions. These factors collectively contribute to depot differences in adipose tissue function and therefore metabolic complications associated with central obesity, especially visceral obesity as well as the protective effects of lower body sc adipose tissue.

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Abbreviations

VAT	visceral adipose tissue
SAT	subcutaneous adipose tissue
sc	subcutaneous
SVC	stromal vascular cells
CLS	crown like structures
LPL	lipoprotein lipase
GLUT4	glucose transporter 4
VLDL	very low density lipoprotein
TG	triacylglyeride
FFA	free fatty acids
TNF-α	tumor necrosis factor-alpha

IL-6	interleukin-6
SAA	serum amyloid A
RBP4	retinol binding protein 4
MCP-1	macrophage chemoattractant protein-1
CRP	C-reactive protein
GM-CSF	granulocyte-macrophage colony stimulating factor
TSP-1	thrombospondin 1

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Biographies

Mi-Jeong Lee earned her Ph.D. from Rutgers, the State University of New Jersey in 2005, where she studied the nutritional regulation of leptin production. She continued her post-doctoral training in the division of Endocrinology, Diabetes and Nutrition at the University of Maryland, School of Medicine, where she focused on depot differences in glucocorticoid action in human adipose tissues. She is currently an Instructor in Medicine in the Section of Endocrinology, Diabetes and Nutrition at the Boston University School of Medicine where she continues this work.

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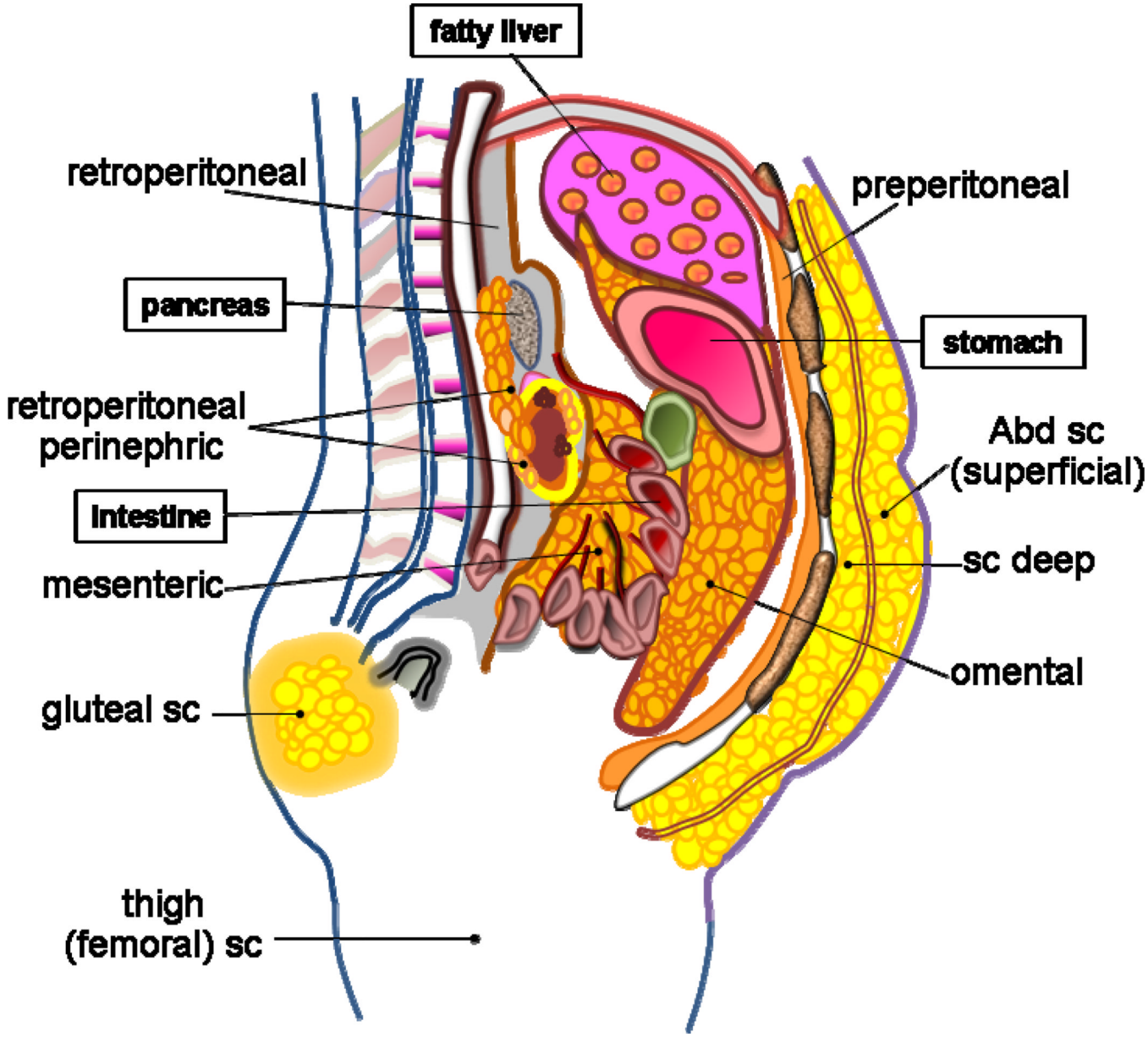

Figure 1. Major adipose depots in humans

Subcutaneous adipose tissues include abdominal and gluteal, as well as femoral. Visceral adipose tissues are associated with digestive organs. Omental is attached to the stomach and mesenteric and epiploic are associated with the intestine and colon respectively. Peripheric fat surrounds the kidney and retroperitoneal fat is located in the retroperitoneal compartment.

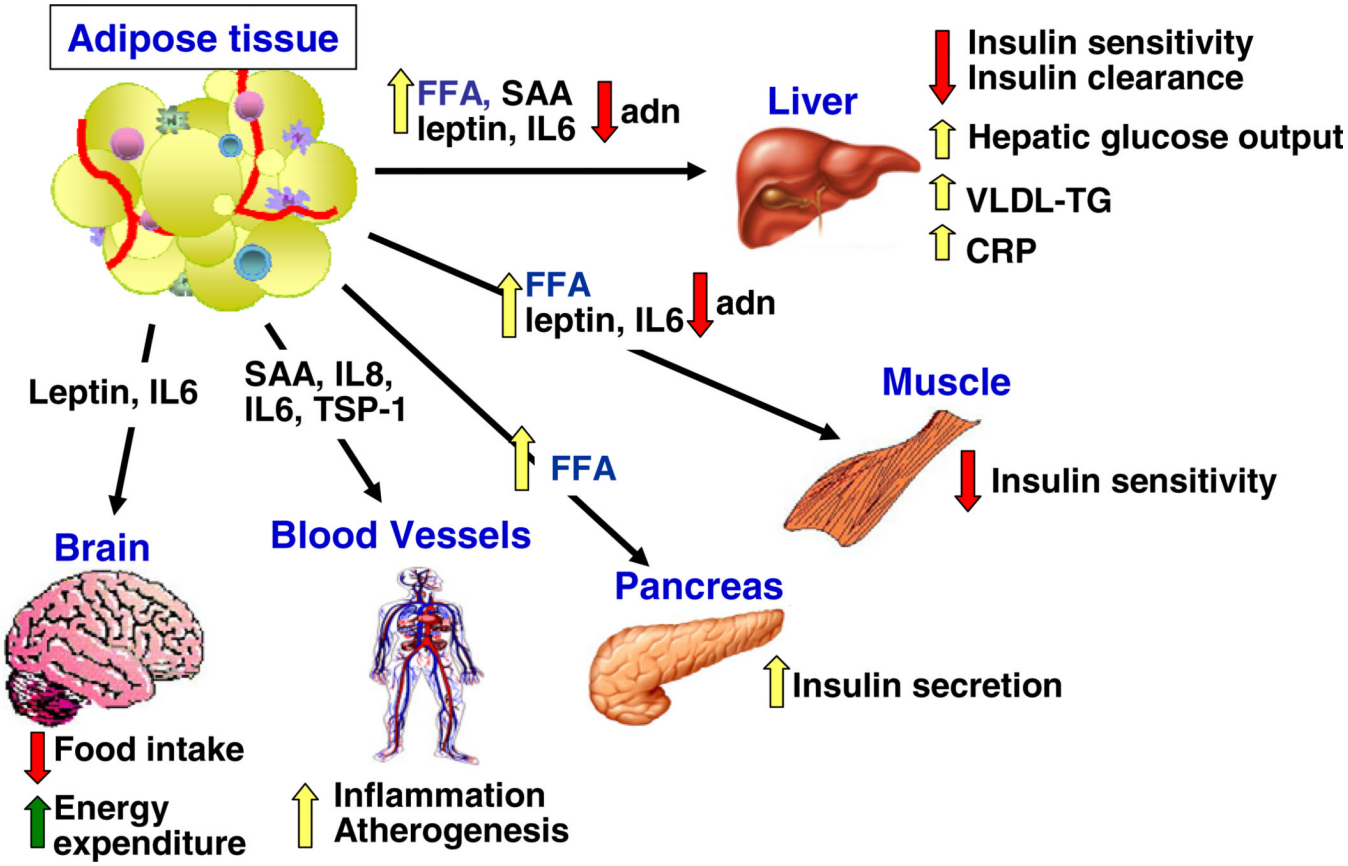

Figure 2. Adipose signals influence systemic metabolism and appetite

Dysfunctional adipose tissue in obesity produces more proinflammatory factors (e.g. FFA, SAA, IL-6) and less antiinflammatory factors (e.g. adiponectin). These exacerbate inflammation and hence risk for metabolic diseases by affecting liver, skeletal muscle, beta-cells, as well as blood vessels. Insulin-glucose homeostasis become impaired as results of increased hepatic glucose output and muscle insulin resistance, and basal insulin secretion from pancreas is increased, most likely by FAs. Leptin and perhaps other adipokines normally regulate food intake and energy expenditure through effects on the central nervous system, but this system may become dysfunctional in the obese state. See text for more details.