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WAT is a functional adipocyte?

Christopher D. Church,[1] Mark C. Horowitz[2] and Matthew S. Rodeheffer[1,3,4,*]

[1]Section of Comparative Medicine; Yale University; New Haven, CT USA; [2]Orthopedics and Rehabilitation; Yale University; New Haven, CT USA; [3]Departments of Molecular, Cell, and Developmental Biology; Yale University; New Haven, CT USA; [4]Yale Stem Cell Center; Yale University; New Haven, CT USA

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In vertebrates, adipose tissue is the main storage site for lipids within specialized lipid-laden mature adipocytes. While many species have evolved cells capable of lipid storage, the adipocyte represents a unique specialized cell involved in fuel storage, endocrine, nervous and immune function. However, the adipocytes are not the only cell type in mammals that can accumulate lipid droplets. The ectopic accumulation of lipid in non-adipose tissues including the liver, skeletal muscle, bone, pancreas, and heart in combination with its excessive accumulation in adipose tissue contributes to metabolic disease. Determining the lipid processing components that are necessary and sufficiently for lipid accumulation in adipose and non-adipose tissues, in addition to endocrine function, will lead to a clearer definition of an adipocyte.

At the turn of the 20th century it was stated that the adipose tissue of mammals is a specific organ formed from connective tissue and functions only to store and release fat in line with supply and demand.[1] By the middle of the 20th century, adipose tissue was making a historical transition from a passive, inactive connective tissue to a functional tissue:

"*Adipose tissue is not merely a storehouse; it is also a manufacturing plant in active operation, not only producing some or all of its own stored materials but probably conducting other processes not yet revealed to the incurious passers by.*"[2]

Evidence from the last several decades suggest that while adipose tissue size is extremely dynamic with great plasticity, it also participates in energy homeostasis via endocrine, paracrine and autocrine signals. Despite the essential role of adipose tissue in energy metabolism and disease, the processes that govern formation and function specifically in vivo are yet to be fully characterized.

Adipocytes and Adipose Depots

White adipose tissue (WAT) in vertebrates, especially in mammals, birds, reptiles and amphibians, contain classical fat-storing cells. WAT is important for energy storage in addition to serving as a mechanical buffer and heat insulator in the skin. WAT is composed of a heterogeneous population of cells that includes fibroblasts, adipocyte precursors, endothelial cells, immune cells, and lipid-filled mature adipocytes.[3] WAT is compartmentalized into distinct depots through the body including several subcutaneous WAT (SWAT) and visceral WAT (VWAT) depots (for a review, see ref. 4) as well as an intradermal layer of adipocytes that is distinct from the SWAT depots.[5] There are also several brown adipose tissue (BAT) depots,[6,7] which are highly specialized tissues that utilize chemical energy stored in lipids to generate heat.[8,9] Since brown and white adipocytes have been shown to come from distinct lineages and mature brown adipocytes can be distinguished by expression of highly specific markers, such as UCP1,[10] this article focuses on WAT.

*Correspondence to: Matthew S. Rodeheffer;
Email: matthew.rodeheffer@yale.edu
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Cellular Lipid Storage

The cellular process of storing triglyceride (TG) in lipid droplets is conserved from yeast, plants, invertebrates and mammals along with many of the molecular processes. Lipid droplets consist of a single phospholipid monolayer that separates the aqueous cytosol from the hydrophobic core containing neutral lipids (TGs) and sterol esters (see refs. 11 and 12 for a recent updates on lipid droplet biology and function).

In eukaryotic cells, cytosolic lipid droplets can range in size from 1 μm in diameter (microlipid droplets in milk-secreting cells) to 200 μm in diameter (very large mature adipocytes).[13,14] Relatively few prokaryotes store neutral lipids (e.g., TG) as most lipid accumulating bacteria and archaea use alternatives such as polymeric lipids including polyhydroxyalkanoates (PHAs) as energy stores under environmental stress such as nutrient limitation,[15] although some Gram-positive bacterial genera including Streptomyces accumulate neutral lipids such as TG and wax esters.[16,17] Plants also have significant lipid-droplet storage depots including the seed, root and leaf,[18] in addition to algae which can store approximately 86% of cell dry-weight as lipid in response to nutrient limitation.[14,19] In yeast, such as *Saccharomyces cerevisiae*, there is very little lipid accumulation in the cytosol (5–10% w/w).[14,20,21]

Metazoans such as *Caenorhabditis elegans* accumulate lipid droplets in fat storing cells of the gut epithelium.[22] Invertebrates, such as *Drosophila melanogaster* are developing as an important model for studying lipid droplet biology and fat cell storage as lipid droplets are distributed throughout the body and accumulate in specialized storage tissues, representing a multifunctional organ involved in growth and reproduction.[23] Vertebrates, such as zebrafish (*Danio rerio*) utilize the liver for lipid droplet storage

representing an adipose store and have recently been shown to express leptin paralogs.[23]

Indeed, leptin, a key endocrine factor secreted by adipose tissue, is integral to food intake regulation in mammals and orthologs have been identified in fish and amphibian species. Xenopus express functional leptin,[24] albeit with low amino acid similarity but identical protein structure, with a potent anorexigenic effect in frogs that is similar to the leptin function in mammals, demonstrating the conserved function of leptin as a pleiotropic signal for appetite, energy balance, development, physiology and behavior (recently reviewed in ref. 25).

Lipid Handling within Cells

As cells accumulate lipid it becomes essential to protect the lipid from degradation and sequester free lipid from the cytoplasm. This is achieved by coating the TG in a monolayer of phospholipid and a spectrum of stabilization proteins such as caveolin and PAT proteins (**P**erilipin, **A**dipophilin, **T**IP47), S3–12 and perilipin 5[26,27] (reviewed in refs. 28 and 29). Larger lipid droplets require adipophilin and perilipin whereas smaller droplets require TIP47 and S3–12.[30] Lipid droplet associated proteins including PLIN1 (Perilipin) and PLIN2 (ADRP, adipophilin) are conserved throughout evolution with PAT-like genes in all unikonts ranging from slime molds to humans.[28,31,32] In addition to these two basic members of the PAT/Perilipin family that are common to all animals, mammals have three additional members (Plin3–5)[33,34] that act as regulators of lipid droplet formation/turnover, suggesting that cytosolic lipid droplets have similar functional lipid machinery components in simple algae to complex metazoans including Drosophila and mammals.[35]

Peroxisome proliferator-activated receptors (PPARs) are ancient nuclear hormone receptors that arised before the divergence of arthropods and vertebrates[36] that are involved in lipid homeostasis and adipogenesis. Gene duplication in vertebrates has led to three distinct isoforms, PPARα, PPARβ and PPARγ, with distinct tissue expression and function.[37,38] PPARγ is a critical adipogenic and lipid homeostatic regulator in addition to being the receptor for the thiazolidinedione (TZD) receptor class of insulin-sensitizing drugs.[39,40] PPARγ expression is 30–40-fold higher in adipose than most other tissues.[41] Furthermore, the PPARγ2 isoform shows adipose-tissue specific expression whereas PPARγ1 is expressed in many tissues.[42] Forced expression of PPARγ in non-adipogenic NIH-3T3 fibroblasts, accompanied by treatment with several activators, induces adipose differentiation and lipid accumulation indicating the key role of PPARγ in lipogenesis.[43]

Hence, lipid droplets are specialized structures required for energy storage expressing the necessary lipid machinery components for the production and release of their lipid cargo. In addition, white and brown adipose depots have evolved as specialized tissues that compartmentalize lipid storage into specific depots and that have unique molecular and endocrine profiles sufficient to modulate whole-body energy homeostasis in response to available metabolic substrates.

The Adipocyte as Functional Endocrine Cell

The classical function of the adipocyte is as a calorie storage system accepting chemical energy in the form of glucose and fatty acid from the blood and converting these metabolites to TG for storage during fed conditions via lipogenesis. During fasting conditions, adipocytes break down stored TGs through lipolysis to produce free fatty acids (FFAs) and glycerol resulting in energy release.[44]

The discovery and characterization of leptin in the mid-1990s as a hormone that is expressed in WAT and functions in the hypothalamus to regulate food intake and metabolism ended the view of WAT as a passive energy reservoir and highlighted the importance of the interaction between peripheral organs and the central nervous system in the control of energy homeostasis.[45]

It is now appreciated that WAT is an active endocrine tissue, with mature adipocytes being responsible for secretion of a number of cytokines (or adipokines) that impact a wide range of physiologic processes, including food intake, energy homeostasis, inflammation, glucose homeostasis, lipid metabolism and angiogenesis. Expression levels of many adipokines are modulated by obesity and are implicated in the development of obesity-associated pathologies, including leptin and adiponectin, which are positively and negatively correlated with the adipose mass, respectively.[46,47] Many adipokines have now been identified and characterized including sex steroids, cytokines (IL-6, TNFα), fatty acids (FAs), components of the complement pathway (acetylation stimulating protein, adipsin), lipoprotein metabolism (LPL, cholesterol ester transfer protein, APOE), proteins that affect cardiovascular function (plasminogen activator inhibitor 1, angiotensogen) or inflammation, growth factors (TGFβ, IGF1) and most recently dipeptidyl peptidase 4 (DPP4[48]) together making up the adipose tissue secretome[49] (reviewed in ref. 50). As adipokines derived from mature adipocytes play such an important physiological role, it is important to understand how adipocytes form and how adipocyte number is regulated. Since mature adipocytes are post-mitotic, they are generated from the proliferation and differentiation of adipocyte precursor cells.

Adipocyte Progenitors (Stem Cells)

The adipose stromal vascular fraction (SVF) has been shown to contain resident 'adipose stem cells,' referred to here as adipocyte progenitors, which can be differentiated down adipogenic, cartilage-forming chondrocyte and osteoblastic bone lineages when induced in vitro with appropriate stimulation.[51] Thus, this highly purified population of cells from the adipose SVF support adipose tissue maintenance and adipose tissue expansion in obesity.

Distinct populations of adipocyte progenitors, isolated from the subcutaneous tissue of mice display a unique cell-surface immunophenotype; negative for the blood lineage ($CD45^-$, $CD31^-$) and positive for mesenchymal stem cell markers (Sca1, CD34, CD24). This specific population of cells (Lin negative, $CD45^-$, $CD29^+$, $CD34^+$, $Sca1^+$, $CD24^+$) can also efficiently

differentiate both in vitro and in vivo.[51] Additional mouse studies have shown localization of similar adipocyte progenitors in the vasculature wall overlapping with pericyte/mural cell markers in adipose tissue.[52,53] Joe et al. also showed that the potency of adipocyte progenitors may depend on their environment and the specific white adipose depot.[53]

Adipocyte Differentiation

Adipogenesis, the formation of specialized mature adipocytes, involves the differentiation of fibroblast-like precursor cells into lipid-laden endocrine cells that can respond to insulin for glucose uptake and lipogenesis and also the secretion of leptin for the control of energy intake. The in vitro differentiation of mouse embryonic fibroblasts (MEFs) and/or adipocyte cell lines such as 3T3-L1 cells have revealed the complex transcriptional cascade necessary for adipogenesis.[54-57] Upon adipogenic stimulation there is a sequential induction of transcription factors (including Klf4, Krox20, CCAAT/enhancer-binding proteins; C/EBPβ and C/EBPδ, for detailed review see refs. 58 and 59). The immature adipocytes then undergo terminal differentiation involving cell-cycle arrest and the induction of peroxisome proliferator-activated receptor gamma PPARγ (specifically PPARγ2) and C/EBPα that leads to the transcription of mature adipocyte genes involved in lipogenesis/lipolysis (e.g., LPL), lipid droplet protection (e.g., perilipin) and adipokine release (e.g., leptin, adiponectin). The final lipid-filled mature adipocyte maintains high expression of PPARγ2.

Despite this detailed understanding of the molecular events controlling adipogenesis in vitro, adipocytes derived from in vitro adipogenesis do not fully recapitulate the characteristics of mature adipocytes in vivo. For example, mature adipocytes have a unilocular morphology with the lipid droplet occupying most of the cell and the nucleus and cytoplasm pushed to the side displaying a signet ring appearance. In adipocytes produced in vitro TG appears in multilocular lipid droplets within the cytoplasm.[54] Additionally, adipogenic cell lines such as 3T3-L1 or 3T3-F442A[60,61] do not recapitulate the high levels of leptin expression detected in vivo.[62] This suggests a requirement for additional factors (e.g., hormone signaling) the ability to sufficiently expand cell size, for which leptin shows a positive correlation, or cell-cell signaling within the heterogeneous cell population of adipose tissue.

Furthermore, in vitro adipogenesis fails to take into account the complex microenvironment in which in vivo adipogenesis takes place. The in vivo environment includes vasculature, nervous innervation, extracellularmatrix (ECM) and resident immune cells, all of which influence in vivo adipogenesis. While gene expression analyses comparing early postnatal mouse adipose development in vivo and 3T3-L1 differentiation in vitro showed a very similar molecular progression to adipogenesis early in development the molecular pathways involving the presence of immune cells were unique to the in vivo development of adipose tissue.[63]

Moreover, the interaction with the ECM including tissue remodeling (e.g., MMP14, TIMP2, TIMP3[64-66]) is necessary for adipocyte expansion in addition to the role of the 3D environment for vasculature in vivo.[67] Additionally, preadipocytes grown in a less dense microenvironment show enhanced adipogenesis compared with denser matrices.[68,69]

The interaction with adipose tissue vasculature may also be an important modulator of adipogenesis in vivo as inhibition of angiogenesis (using TNP-470, angeostatin and endostatin) reduced adipose tissue mass expansion and protected from mice diet and genetic-induced obesity resulting in increased energy expenditure.[70-72] During early postnatal development the inhibition of VEGFA (and placental growth factor) or depletion of macrophages in mice leads to a delay in adipogenesis suggesting an important interaction between angiogenesis and adipogenesis in vivo.[73]

Ectopic Lipid Accumulation

In normal aging and several pathological conditions lipids can become stored in many non-adipose tissues. For example, obesity can lead to the development of insulin resistance, lipid overload (dyslipidemia) and hypertension all of which are linked to the excess accumulation of lipid. Adipocytes have evolved as the primary lipid store and display a great capacity to buffer plasma fatty acids through lipid storage and hypertrophy. Once maximal capacity is reached, in a depot and time specific manner, the net flux of lipids into circulation and non-adipose tissues results in ectopic lipid accumulation in hepatocytes, cardiomyocytes, skeletal muscle, pancreas, adrenocortical cells, thymus, enterocytes and macrophages, which all have the capacity to accumulate large amounts of lipids.[74]

Ectopic lipid storage can result in insulin resistance in the liver and skeletal muscle, impaired cardiovascular function and overall 'lipotoxicity' (lipid accumulation in non-adipocytes as an acquired pathogenic state).[75,76] The accumulation of lipid in non-adipose tissue can occur by two mechanisms: (1) the induction of lipogenic processes within other cell types, as is evident in the formation of lipid droplets within hepatocytes in hepatic steatosis, or (2) the formation of adipocytes within other tissues.

Lipid Accumulation in Non-Adipocytes

While lipid metabolism and lipogenesis are required in all cells for essential functions, such as membrane production and maintenance, there are many cell types that can develop overt lipid droplets either in the course of their normal function or in pathological conditions. Lipid droplet formation within non-adipocytes accompanied by the expression of gene programs that are often considered adipocyte-specific. A few such examples of non-adipose lipid accumulation are discussed below.

Liver TG content is increased in subjects with insulin resistance and metabolic syndrome.[77,78] TG in the liver can be derived from diet, de novo synthesis or adipocytes (for a recent review, see ref. 79) During its early stages lipid is deposited in the cytoplasm of hepatocytes progressing toward steatosis (> 5% lipid droplets in hepatocytes or > 55 mg per g of liver).[79,80]

Steatotic hepatocytes display many cellular and molecular similarities to traditional WAT-resident mature adipocytes. As

hepatic steatosis progresses, both PLIN1 (normally associated with larger lipid droplets) and PLIN2 (ADRP) expression are increased and this increase is associated with the ballooning of hepatocytes.[81] Liver TG is positively associated with the expression of FABP4, LPL, ACSL4, PLIN1 and PPARγ2[78,82] and genes involved in both lipid and carbohydrate metabolism. However, similar to lipid filling of 3T3-L1 cells in vitro, liver TG accumulation and leptin expression are not correlated.[61,78]

The expression of PPARγ2 is especially interesting as this isoform is normally restricted to expression in adipocyte lineage cells. Upregulation of PPARγ is linked to increased steotosis by the activation of lipogenic genes, de novo lipogenesis and increased hepatic triglyceride accumulation.[77,83-86]

Adiponectin receptors AdipoR1 and AdipoR2 mediate the insulin sensitizing role of adiponectin.[46,87] Overexpression of adiponectin, AdipoR1 or AdipoR2 in the liver reduces hepatic ceramide levels and improves insulin sensitivity.[88] Adiponectin is relatively abundant and specifically secreted from adipose tissue with relatively high circulating levels;[89] however, much like the lack of leptin expression in steatotic hepatocytes, high fat diet feeding-induced lipid accumulation does not induce the expression of adiponectin in fatty liver.[90]

Based on these studies, the molecular signatures of mature adipocytes and steatotic hepatocytes are similar in terms of expression of genes involved in lipid filling. However, steatotic hepatocytes and other lipid filled non-adipose cells fail to express the full repertoire of proteins associated with an adipocytes endocrine function such as leptin and adiponectin. Furthermore, a similar expression pattern is revealed from in vitro adipogenesis suggesting a unique program is required for a functional endocrine adipocyte.

Lipid droplets also form within skeletal myocytes. Skeletal muscle is the primary target of insulin and reduced insulin sensitivity in muscle leads to diminished post-prandial glucose clearance and consequently systemic hyperglycemia.[91-93] Skeletal muscle utilizes FAs as an important metabolic substrate for physical activity and leptin stimulates AMPK, PI3K signaling for the cycling between de novo lipogenesis and lipid oxidation, hence protecting skeletal muscle from TG accumulation.[94,95] However, excess circulating lipid can lead to the excessive accumulation of lipid droplets within skeletal muscle[96] in the form of intramyocellular TG (IMTG) (see recent review in ref. 97). IMTG accumulation usually correlates with body and tissue insulin resistance,[98-100] but there are some situations in which skeletal muscle can cope with excess lipid.

Exercise training enhances lipid tolerance as elite endurance athletes have high levels of IMTG and diacylglycerol (DAGS), yet are extremely insulin sensitive.[100-103] While the specific gene programs of lipogenesis within skeletal myocytes remain unclear, under normal conditions myocytes express PPARγ and the PAT proteins ADRP and TIP47.[104,105] In addition, PPARγ function in skeletal myocytes is required for normal glucose homeostasis and proper regulation of body weight.[106] Other muscle cell types, such as cardiomyocytes and smooth muscle cells, can accumulate significant amounts of intracellular TG which also corresponds with the expression of PPARγ and PAT proteins.[107-109]

The association of PPARγ expression with lipid accumulation and droplet formation is common and reaches beyond the cell types described here, encompassing macrophages (foam cells) and even pancreatic β-cells.[110,111] As PPARγ is considered a master regulator of adipogenesis, and expression of PPARγ in non-adipogenic fibroblast cell lines leads to the accumulation of lipid,[43] the correlation of PPARγ expression with lipid accumulation is not surprising. Moreover, the potent lipogenic effects of PPARγ makes it likely that lipid accumulation upon treatement with PPARγ agonists, such as thiazolidinediones (TZDs), simply indicates that the cells being studied express functional levels of PPARγ. In support of this, treatment of KKA^{y} mice, which express PPARγ in hepatocytes, with TZDs results in hepatic steatosis.[112]

Ectopic Adipocytes

Another source of lipid accumulation in tissues is the formation of lipid-filled cells that are either derived from precursor cells that have the characteristics of adipocyte progenitors or from unknown cell sources.

Duchenne muscular dystrophy is associated with adipocyte accumulation and scar tissue within skeletal muscle with the progression toward sarcopenia resulting in reduced muscle mass and function which is also observed in elderly, obese and sedentary individuals.[113,114] Adipocyte accumulation is also observed in the skeletal muscle of mice lacking *Myf5*, a key myogenic determination gene, in addition to fibrosis and perturbed muscle regeneration.[115] Adipocyte precursor and fibrocyte (fibro/adipogenic progenitors, FAPs) cells that are distinct from muscle progenitors (satellite cells) have recently been identified and isolated from within skeletal muscle, and they may promote muscle differentiation by regulating muscle precursor cells.[116,117] FAPs show a similar cell surface immunophenotype marker profile to that of adipocyte progenitors that have recently been identified in WAT.[51,52] However, FAPs do not express mural/pericyte markers like mouse adipocyte precursors.[52,116,117] Crosstalk between cells of the skeletal muscle lineage and the FAP lineage are involved in the full maintenance and regeneration of skeletal muscle in vivo. Thus, the presence of adipocytes, derived from skeletal-muscle resident mesenchymal/adipocyte precursors in skeletal muscle provides essential cross talk between cell types both to promote skeletal muscle regeneration and pathological changes associated with aging.[116,117] Regulatory functions for adipocyte precursors have also been identified in the skin,[5] suggesting that adipocyte precursors may have the ability to affect their niche in other microenvironments.

Another site of adipocyte formation is the bone marrow. Adipocytes were identified in the bone marrow (BM) more than a century ago, but unlike adipose tissue in other depots, these cells have never been considered more than "fillers" or a default for other "more important" BM components.[118]

Increased marrow adiposity is reported to be a strong risk factor for subsequent osteoporotic fractures and is inversely associated with bone mineral density.[119-122] Furthermore, BM adipocytes increase with age as bone mass decreases.[123] Commonly used drugs

such as glucocorticoids and TZDs induce progressive marrow adiposity accompanied by rapid bone loss.[124] Recently, it was reported that girls with anorexia nervosa (AN) and very low body weight have markedly increased marrow adiposity that is linked to uncoupled bone remodeling and high circulating levels of Pref-1, a preadipocyte factor that inhibits adipogenesis.[125,126] Moreover, mice on a calorie restricted diet have reduced body fat, increased BM adipocytes and low bone mass.[127,128] The presence of marrow adiposity in several conditions that lead to decreased levels of WAT suggest that the regulatory mechanisms of marrow adipocyte accumulation may be distinct from adipogenesis in WAT.

Gene profiling comparing adult mouse derived BM adipocytes to epididymal adipocytes[129] showed that BM adipocytes have low expression of adipocyte specific genes (e.g., PPARγ, FABP4, perilipin) and high expression of genes associated with early adipocyte differentiation (C/EBPβ, RGS2). Which regulate bone cell function were also markedly upregulated in BM adipocytes. These cells may derive from a progenitor that is distinct from the one that gives rise to either WAT or BAT, whether the marrow adipocyte progenitor shares a common progenitor with osteoblasts remains to be shown in vivo.

Conclusions

Many cell types can uptake and process lipid. The WAT adipocyte has many traits that are common between cells that accumulate lipid including non-adipose tissue cells in healthy and disease states. Thus, the factors likely to define an adipocyte must go beyond those involved in the capacity to store lipid. This can be considered in a hierarchical manner ranging from simple storage to active storage with endocrine function and distinct molecular signatures, physiology and depots throughout the body. In order to define a WAT adipocyte we propose that in addition to the evolutionary conserved lipid machinery components required to process and store lipid such as PAT proteins and lipogenic/lipolytic enzymes (fatty acid synthetase/lipase) it is necessary to consider additional factors such as adipokines (e.g leptin and adiponectin), and the factors required for leptin and adiponectin expression, in relation to physiological levels and function. Understanding the factors required for adipogenesis and the interaction of adipocytes with additional cell types and tissues in a systems biology approach will be key to revealing the full in vivo function and defining characteristics of an adipocyte.

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