Chapter 3
Adipose Tissue Development, Structure and Function

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Multiple Functions of Adipose Tissue

One of the earliest reports of adipose tissue was made by the Swiss naturalist Conrad Gessner in 1551 (as translated by Cannon and Nedergaard [1]). However, the notion that adipose tissue was composed of living lipid-laden cells was hotly debated [2]. The past decades have seen a remarkable increase in our understanding of adipose biology and obesity (Fig. 1). This trend is undoubtedly driven by the global epidemic of obesity and associated diseases. Adipose tissue is designed to function as the main long-term fuel-handling organ, and actively controls energy homeostasis. Adipose tissue stores excess fuel in the form of triglycerides and relinquishes these reserves during periods of nutritional deprivation. In homeotherms, adipose tissue also plays equally important roles in thermoregulation through both its insulatory properties and ability to generate heat via non-shivering thermogenesis. In addition to these energetically important functions, the mechanical properties of adipose tissue allow it to protect various organs from injury. To perform these multiple tasks, adipose tissue depots have developed characteristics that can be variable, adaptable and complex.

Biochemical Properties of Adipocytes

As the major functional component of adipose tissues, adipocytes express the cellular machinery that enables their biochemical functions. Adipocytes can take up free fatty acids (FFAs) (through specific cell surface transporters and intracellular fatty acid binding proteins), and synthesize FFAs via de novo lipogenesis. The FFAs are then esterified with glycerol to form triacylglycerols (TGs), which are then stored

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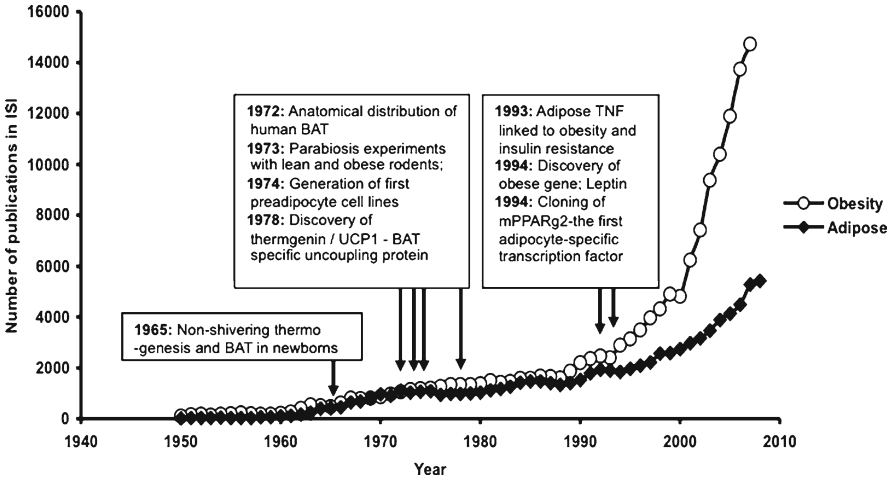

Fig. 1 Chart showing the dramatic recent increase in the annual number of publications containing the words "Obesity" or "Adipose" (from ISI for 1950–2008). Similar trends were identified when searching PUBMED and Scopus. Also indicated is the timing of some seminal discoveries that have influenced the field of adipose tissue biology

in lipid droplets. Associated with these lipid droplets is a biochemical machinery that facilitates the break down of TGs into glycerol and fatty acid. FFA derived from adipose lipolysis are released into the circulation, and used for fatty acid oxidation in the liver, muscle and other organs. Adipocytes are sensitive to hormonal stimulation, and respond to both anabolic and catabolic hormones, such as insulin, IGF, glucagon and catecholamines. On the other hand, adipocytes synthesize and secrete numerous proteins that impact with potent local and systemic actions.

Adipose Tissue is Connected to Other Physiological Systems

The functions of adipose tissue can vary depending on the type of adipose tissue and the anatomical location. The specific adipose tissue types and depots are discussed in greater detail below. Another fundamental aspect of adipose tissue is that its function is intricately linked with whole-body metabolism and nutritional status. Adipose tissue is not only capable of responding to neural, hormonal and nutritional signals, but can also secrete paracrine and endocrine signals. In so doing, adipose tissue has a major impact on appetite regulation, thermoregulation, immunity, reproduction, cardiovascular system, bone biology, wound repair, respiratory system and sleep.

Dysregulation of adipose tissue has been associated with a variety of pathological states, the metabolic syndrome, type 2 diabetes, atherosclerotic cardiovascular diseases, neurodegenerative diseases, non-alcoholic fatty liver disease, cancer,

polycystic ovary syndrome, and sleep apnoea. The recognition of links between adipose tissue and disparate pathologies has ignited the current interest in adipose tissue and adipocyte biology.

The connection of adipose tissue with other physiological systems is mediated by the ability of adipose tissue to regulate energy availability and by its ability to communicate with other organs. Adipose-secreted proteins, known as "adipokines", include hormones, proinflammatory cytokines, growth factors, complement factors, matrix metalloproteins and several types of binding proteins (e.g. lipocalins, IGFBPs, SFRPs). Adipose tissue also produces non-protein species, such as fatty acids, steroid hormones, prostaglandins and retinoids [3].

Anatomical Distribution and Structure of Adipose Tissue

At first glance adipose tissue can be mistaken for an amorphous collection of lipid droplets loosely held together by connective tissue. However, adipose structure is more complex. In mammals, adipose tissue develops in many sites throughout the body, occurring in areas of loose connective tissue, such as subcutaneous layers between muscle and dermis. Adipose tissue also forms around internal organs, such as the heart, kidneys and pancreas. Adipose tissue is also found in the bone marrow. These disparate locations suggest that the ontogeny of the adipose tissue may vary, and that each depot may be functionally distinct.

The most popular classification of adipose tissues used in homeotherms divides adipose tissue into "white" and "brown", based on appearance (Fig. 2). White adipose tissue (WAT) is visually more distinct, and is the predominant site of lipid storage and FFA release via lipolysis. In contrast, brown adipose tissue (BAT) is denser and highly vascularized, hence, its brownish coloration. The primary function of BAT is in energy dissipation through non-shivering thermoregulation. Both types of adipose tissues are further sub-classified based on their anatomical location. In humans WAT is spread throughout the body, with major intra-abdominal/visceral

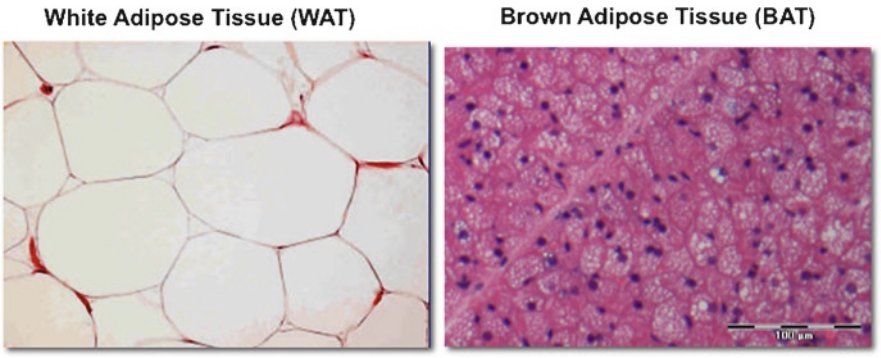

Fig. 2 Haematoxylin–eosin stained sections of white and brown adipose tissues

depots around the omentum, intestines, perirenal areas, as well as in subcutaneous depots in the buttocks, thighs and abdomen. WAT can additionally be found in areas as diverse as the face and extremities, in the retro-orbital space and in the bone marrow. In contrast, BAT depots are typically located in the paraaortic region, mediastinum, neck, perirenal and interscapular regions. Studies have also compared WAT depots and shown that despite their relatively conserved morphology, different WAT depots exert distinct metabolic features. For example, excessive accumulation of visceral WAT is associated with insulin resistance, diabetes, dyslipidaemia and higher risk of atherosclerosis [4].

The histology of WAT has received much attention, particularly in the last few years, following the demonstration that WAT has its own population of resident adipose tissue macrophages (ATMs). The extent of macrophage infiltration of WAT and levels of chemokines and pro-inflammatory cytokines correlates strongly with obesity and glucose intolerance [5, 6]. By far the largest amount of WAT in a lean people is composed of unilocular adipocytes with diameters ranging from 20 to 200 μm. In larger white adipocytes, the unilocular lipid droplets occupy ~90% of the cell volume, thus compressing the nucleus and cytoplasmic organelles into the periphery of the adipocyte. Smaller (<20 μm) adipocytes are less visible in histological sections, but have been reported to cluster near sites of angiogenesis in WAT, and appear as immature multilocular adipocytes.

WAT comprising mostly of smaller adipocytes is associated with improved insulin sensitivity. However, the quality of types of lipids stored within adipocytes, irrespective of size, may also be an important indicator of adipose tissue function [7]. Typically, unilocular WAT adipocytes are composed of neutral TGs derived from oleic and palmitic acids. However, diacyglycerols, phospholipids, unesterified fatty acids and cholesterol are also detectable. WAT contains non-adipocyte cells that make up the stromovascular fraction (SVF). Among these are vascular endothelial cells, immune cells and vascular smooth muscle cells. Some of these cells have been implicated in the paracrine signalling events that control adipose tissue expansion [8, 9].

The kinds of immune cells being discovered in WAT is increasing as better tools for identification and isolation become available. In particular, the proinflammatory ATMs have been the subject of intense research. However, the ATM population is more diverse and at least three subtypes have been reported: the resident macrophages, pro-inflammatory (M1) and pro-fibrotic (M2) [10, 11]. Collectively, the ATMs play a significant role in the endocrinology and proper function of adipose tissue [12]. Indeed, the relative proportions present in a given WAT depot correlate with the degree of obesity and insulin resistance. That being said, additional immune cell types are also recruited into WAT, and while the full complement remains to be established, it does include monocytes [13, 14] and T lymphocytes [15].

WAT is innervated by sympathetic nerves which are present in the SVF. An increase in sympathetic activity stimulates lipolysis and FFA release. Another important non-adipose component of the SVF is the connective tissue and extracellular matrix (ECM). Collagen and elastic fibres and resident fibroblasts maintain

ECM integrity. On the whole, the ECM provides a structured mesh which binds the cellular components of adipose tissue, and creates a defined tissue mass, thereby defining the boundaries of individual adipose tissue depots, but allowing a close association with neighbouring organs.

Among the SVF cell types, arguably the most interesting are the progenitors, known as mesenchymal stem cells (MSCs), and sometimes referred to as adipose stem cells, mural cells or pericytes. MSCs can differentiate into mature adipocytes, and thus serve as an important source for new preadipocytes required for adipose tissue expansion. However, MSCs are also pluripotent and have the potential to develop into chondrocytes, osteoblasts, myoblasts, hepatocytes [16], neural cells [17], endothelial cells [18], macrophages [19] and megakaryocytes [20]. This aspect continues to fuel an ongoing debate regarding the similarities between macrophage and preadipocytes, and whether they belong to a common lineage or exhibit convergent functions [21–24]. Nonetheless, taking a broader perspective, it is clear that the pluripotency of adipose-derived stem cells hold the key for determining the potential of adipose tissue expansion. Not only are MSCs a source of new adipocytes, but MSCs have the potential to regenerate new blood vessels that may have been lost as a result of adipose tissue death. MSCs are attracting much attention because of their potential use in regenerative medicine [25, 26].

In Vivo Regulation of WAT Expansion

WAT expansion occurs as the combined result of two processes: enlargement of existing adipocytes (hypertrophy) and formation of new adipocytes (hyperplasia). However, the fundamental prerequisite for adipose tissue expansion is existence of an energy surplus and hence the need storage. Adiposity can be affected by genetic and environmental factors. The best characterized environmental factors are the overconsumption of energy-dense foods and sedentary lifestyle. Some drugs, notably thiazolidinediones, insulin glucocorticoids, oestrogen, atypical antipsychotics, antidepressants, and anticonvulsants, can increase body fat. Ageing, gender and ethnicity also influence adiposity but the molecular basis is unclear. Genome-wide association studies have discovered genes that alter appetite and adiposity [27, 28]. Epigenetic factors can also affect the development of adiposity [29], and some studies have linked in utero and early life events to obesity and metabolic syndrome [30, 31].

While these studies may identify new factors associated with increased risk of obesity, there are critical questions to be addressed. How does adipose tissue sense nutritional surplus, and how is this information transduced into adipose expansion? What are the molecular determinants of adipose expansion in obesity? Do specific signalling molecules facilitate the recruitment of new adipocytes during tissue hyperplasia? These fundamental aspects of the adipose tissue biology may hold the key to unveiling the association between obesity and the metabolic syndrome.

Regulation of White Adipocyte Differentiation

Adipocyte differentiation is an important component of adipose tissue hyperplasia. The programme of adipocyte differentiation or adipogenesis is much more than an enhanced process of lipid accumulation (i.e. lipogenesis). Adipogenesis represents the orchestrated differentiation of proliferating fibroblast-like preadipocytes into non-proliferating, lipid laden, hormonally responsive and functional adipocytes (Fig. 3). Much of what we know about the molecular regulation of adipogenesis comes from in vitro studies that utilize either immortalized cell lines or primary cultures of freshly isolated MSCs from adipose tissue. The vast majority of these precursor cells require induction with a chemically defined adipogenic cocktail. These in vitro models cannot recapitulate in vivo adipose tissue expansion per se; nonetheless, they have allowed the manipulation from mechanisms underlying adipocyte differentiation, thereby increasing our understanding of the molecular basis of this developmental programme. Indeed, the need for specific adipogenic induction reagents is consistent with the notion that adipogenesis is not a spontaneous process, but one that requires a tightly regulated hormonal mellieu [32]. Another advantage of in vitro models is that the homogeneous preadipocytes are amenable to the study of the temporal aspects of adipocyte differentiation, some of which are transient or cell autonomous.

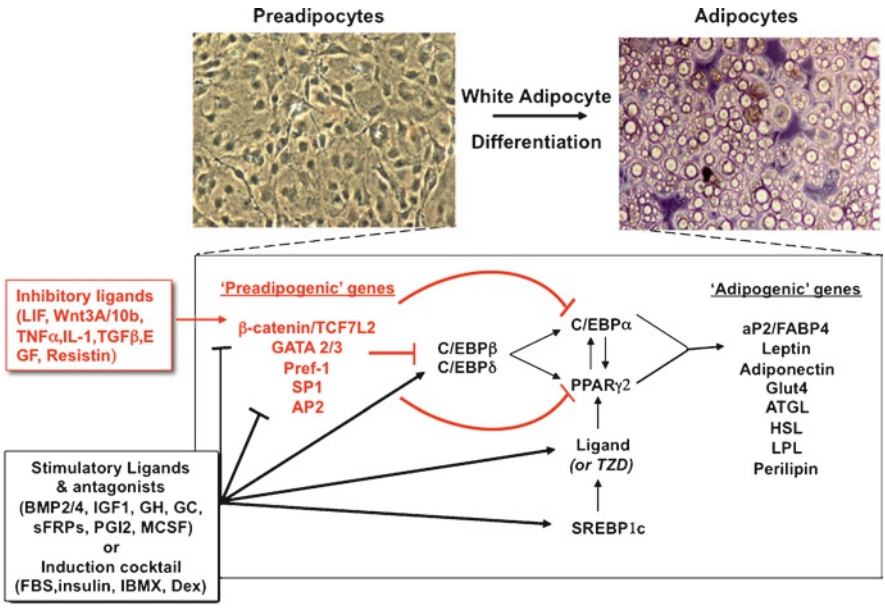

Fig. 3 Differentiation programme for white adipocytes

This is best detected in synchronized and homogenous cell populations [33–37]. PPARγ and C/EBPα are the key adipogenic transcription factors needed to drive the expression of genes to convert preadipocytes into non-proliferating, lipid-laden adipocytes [37, 38].

However, the in vitro models do not enlighten us about how adipocyte recruitment is regulated in heterogeneous tissue. It is clear that in vivo, adipogenesis is not a synchronous phenomenon, recruiting all progenitors into the adipogenic programme during a defined developmental stage. Rather adipose tissue retains a population of stem cells which replace dying adipocytes. Indeed, it has been suggested that ~10% of the body's adipose cells are regenerated each year [39]. However, the nature of the signals that prevent all MSCs from being recruited and control the extent of adipocyte differentiation despite excessive nutritional stimulation are unknown. An attractive hypothesis is that adipogenesis is carefully titrated by specific local paracrine and autocrine signals that are both cell-specific and regulated by physiological and nutritional cues. A possible candidate is the Wnt signalling network, which comprises of a host of ligands, antagonists and receptors that are secreted in a cell-specific manner. They often act in a paracrine/autocrine manner and have been implicated not only in both titrated developmental programmes but also in adult tissue remodelling. Until recently, Wnt/β catenin signalling has been implicated in lineage determination of MSCs, promoting bone and muscle development while inhibiting adipogenesis [40, 41]. We have identified Dapper1 (DACT1) as a preadipocyte gene that is required for adipogenesis. DACT1 is an intracellular scaffold protein whose cellular levels appear to modulate Wnt/β-catenin signals. During adipogenesis, DACT1 inhibits Wnt/β-catenin signalling primarily through paracrine and autocrine mechanisms, by controlling the production of key Wnt ligands and antagonists. Importantly, the relative expression of DACT1, Wnt ligands (Wnt10b and Wnt3A) and Wnt antagonists (sFRP1–sFRP5) are both cell-type specific and also regulated in vivo by nutritional status, pharmacological stimulation and during the development of dietary and genetic obesity [42]. A biochemical pathway that may link cellular glucose sensing and the Wnt/β-catenin signalling has also recently been reported in macrophages [43]. Furthermore, the paracrine actions of endothelial-derived factors have been shown to inhibit adipogenesis in part via induction of Wnt ligand expression in adipose stromal cells [9]. Taken together, a picture is now emerging to suggest that the Wnt/β-catenin signalling network may hold the molecular key to the physiological regulation of adipose tissue expansion in vivo.

Several lines of evidence now suggest that obesity-associated metabolic dysregulation is mediated by inflammation, at least partly, by limiting adipose tissue expansion [44–48]. Given that a number of pro-inflammatory cytokines, including TNF-α and IL-1β are potent inhibitors of adipogenesis, it has been proposed that these signals may interact with Wnt/β-catenin [49, 50]. By limiting the production of new and smaller adipocytes and adipose tissue expansion, pro-inflammatory cytokines may accelerate the progression of insulin resistance and prediabetes to overt diabetes [51].

Identification of White Adipocyte Progenitors

The non-synchronous nature of adipose differentiation in vivo has made it difficult to dissect out homogeneous regions of specific precursor cells from embryos or adult tissues and study these ex vivo. Instead, many studies have used mixed populations of MSCs derived from adipose SVF or pluripotent murine embryonic fibroblasts to study adipogenesis. A few groups have used immortalized and/or subcloned adipogenic cell lines [36]. However, Rodeheffer and colleagues have recently used serial fluorescence-activated cell sorting to deplete SVF of cells from endothelial and haematopoietic lineages (using CD31, CD45, Ter119) followed by positive selection for three stem cell antigens (CD29+:CD34+:Sca-1+). In so doing, they isolated a subpopulation of SVF cells that exhibited enhanced lipogenic potential in vitro, formed unilocular adipocytes and represented 53.5% of SVF cells. A final selection for CD24-positive cells isolated a much smaller population (0.08% of total SVF cell number) and these were also capable of forming functional adipose depots in vivo [52]. It is noteworthy that the enhanced adipogenic capacity of Lin–:CD29+:CD34+:Sca-1+ cells in comparison to SVF is consistent with the notion that in vivo negative regulation of adipogenesis is mediated via paracrine signals between heterogeneous cell populations. This is further supported by the observations that like 3T3-L1 preadipocytes, these enriched primary adipocyte precursors do not differentiate when implanted into wild-type mice but require a proadipogenic environment [52]. Although the molecular basis for this is not understood, it is likely that such an environment requires not only a nutritional surplus but appropriate proadipogenic cues derived from endocrine and paracrine sources.

Early light and electron microscopic studies of putative adipocyte precursors had some success in identifying adipocyte progenitors in whole adipose tissue [53]. Recent studies have shown that immature adipocytes cluster near sites of angiogenesis suggesting that that in vivo, adipogenesis and angiogenesis are causally associated [54, 55]. An increase in in vivo neovascularization precedes adipogenesis [56], and this process is in turn regulated by hypertrophic adipocytes [8].

It appears that pericytes found closely associated with blood vessels may in fact represent a subpopulation of adipocyte progenitors. Evidence for this has come from elegant studies using a transgenic approach to generate various PPARγ-reporter mice [55]. PPARγ-positive pericytes retained the ability to proliferate. These cells can be detected prenatally and proliferate during the first month of life, a time when white adipose depots expand. PPARγ-positive SVF cells from 30-day-old mice can also form adipose depots when injected subcutaneously into nude mice. As with the precursors reported by Rodeheffer et al. [52], this SVF subpopulation also expresses stem cell markers Sca1+ and CD34+ but are negative for CD105 (Endoglin), CD45 (protein tyrosine phosphatase, receptor type, C), TER119 (lymphocyte antigen 76), and Mac-1(CD11b or integrin alpha M). Gene expression profiling of the PPARγ-positive SV cells confirmed that they have a preadipocyte-like signature and are distinct from mature adipocytes. These progenitors expressed developmental transcription factors (e.g. goosecoid and twist2), ECM genes (e.g. MMP3) and

anti-angiogenic factors (e.g. Stab1) and signalling receptors (e.g. EGFR and FGF10). Gene expression data are also emerging to suggest that precursors from different WAT depots exhibit distinct transcriptional profiles [57].

These data indicate that the regulation of adipogenesis in vivo is dependent on an intricate interplay between hypertrophic adipocytes, differentiating adipocytes and developing vasculature. This allows for adipogenic potential, storage capacity and nutritional supply to be efficiently but tightly regulated. Potentially, adipose expansion could be manipulated in various depots for the prevention and treatment of diseases associated with obesity [58].

Brown Adipose Tissue

BAT primarily functions as a thermogenic tissue in response to sympathetic nerve activity [59]. BAT is composed of lipid-laden adipocytes, blood vessels and nerves. However, the cellular heterogeneity of BAT is less well characterized than that for WAT (Fig. 4). In contrast to the unilocular white adipocytes, brown adipocytes are smaller (<20 μm) multilocular cells with eccentrically located nuclei, and are often so densely packed that it can be difficult to distinguish individual cell boundaries (Fig. 4). Brown adipocytes also have large numbers of mitochondria – the site of thermogenesis. Brown adipocytes are also characterized by the unique expression of the mitochondrial uncoupling protein (UCP)-1. BAT is metabolically very active,

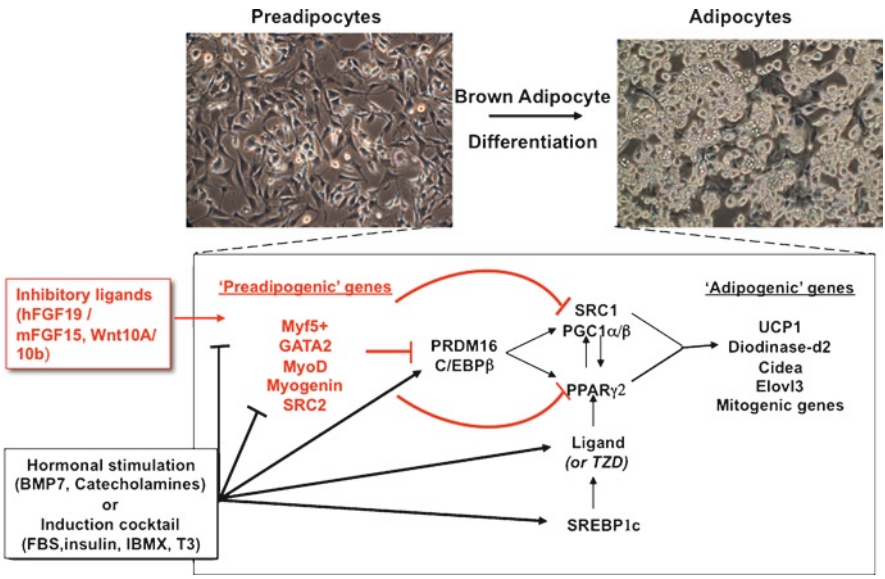

Fig. 4 Differentiation programme for brown adipocytes

consuming more glucose per gram of tissue than muscle. Indeed, this level of activity only occurs with the brain and tumorigenic tissues.

In Vivo Regulation of BAT

BAT depots also have a remarkable ability to expand and contract in response to thermogenic demands. The expansion and activation of brown fat is stimulated in vivo by chronic cold exposure. Certain high-fat diets that cause overfeeding in rodents (cafeteria diets) can also stimulate the expansion and activation of brown fat. This so-called diet-induced thermogenesis may represent a physiological attempt to restrain weight gain and obesity [60]. BAT is increased by thyroid hormones, which promote non-shivering thermogenesis, and chronic adrenergic stimulation. Factors that stimulate vascularization (e.g. angiopoietin-2) in adipose tissue have also been shown to be important in BAT expansion. Furthermore, Wnt10a [61], Wnt10b [62], FGF19 (FGF15 in mouse) [63, 64] and BMP7 [65], have all been shown to increase BAT. The expansion and activation of BAT is accompanied by stimulated mitochondrial biogenesis and oxidative metabolism.

The programme of brown adipocyte differentiation includes activation of thermogenic genes (UCP-1, PGC-1α and Deiodinase-D2), mitochondrial genes and other BAT-selective genes (e.g. cidea and elovl3) [66–68]. This occurs in addition to the expression of many adipogenic genes reported for white adipocytes. The transcriptional control of BAT development and differentiation has recently been reviewed in detail [69]. In summary, while BAT has some similarities with the gene expression profiles exhibited by differentiating white adipocytes, it is clear that the programme of brown adipocyte differentiation is distinct. For example, ectopic expression of PPARα or C/EBPα in mesenchymal cells induces white, and not brown adipocyte differentiation.

Recently, a nuclear scaffold protein, PRDM16, has been shown to drive BAT cell differentiation and function [68]. PRDM16 regulates the co-activators PGC-1α and PGC-1b, as well as the transcription factors, PPARα and PPARγ, which collectively induce brown fat cell-selective genes. PRDM16 expression is also associated with the suppression of several white adipocyte genes (i.e. resistin and angiotensinogen), as well as muscle cell-selective genes (i.e. myoD, myogenin and myosin heavy chain). The former appears to require interaction between PRDM16 and the co-repressors, CtBP1 and CtBP2 [66]. These studies have therefore identified a new molecular determinant of brown adipose differentiation and also provide significant support for the existence of a distinct cellular lineage of progenitors that can form new brown adipocytes.

A longstanding debate in BAT biology is whether brown adipocytes are derived from a distinct lineage, share a common lineage with white fat cells or transdifferentiate from existing mature white adipocytes. This debate is fuelled in part by the fact that in addition to defined BAT depots, traditional WAT depots also have the capacity to adopt some key phenotypic characteristics of BAT albeit under

specific circumstances. Indeed, β-adrenergic signalling in WAT promotes the appearance of brown fat cells and the increased and sustained expression of C/EBPb in white fat cells has been shown to promote the expression of brown fat cell selective genes [70]. There is also evidence that this capacity may be genetically determined. Whether this represents trans-differentiation, induction of a common functional phenotype or recruitment of pluripotent MSCs remains unclear.

Nonetheless, a recent study provides compelling evidence to suggest that BAT is likely to be derived from a distinct lineage and may share a common ontogeny with muscle progenitor cells. Seale et al. found that primary brown fat progenitors lacking PRDM16 exhibited greater potential for skeletal muscle differentiation. Conversely, overexpression of PRDM16 in myoblasts promoted brown adipocyte differentiation [67]. Additional compelling evidence comes from Myf5-lineage tracing studies that showed that brown fat and skeletal muscle, but not white fat, can be generated from Myf5-expressing progenitors [67]. However, much remains to be done before the debate surrounding the identity and ontogeny of the brown adipocyte progenitor is settled [71]. The association between BAT and muscle may be physiologically significant, since the presence of ectopic BAT in muscle explains the species-specific differences in risk of metabolic syndrome in mice [72].

Recent Advances in Human Adult BAT

Until recently, it was believed that the presence of BAT was limited to rodents and newborn human infants, where BAT regulates thermogenesis. However, it is now clear that BAT can persist in human adults in variable amounts [73]. The breakthrough has come with the aid of a technique isotopic tracer, 18F-fluorodeoxyglucose (18F-FDG), combined with computed tomography (CT). This technique is used routinely to identify malignant metastatic tissues in the clinic. However, in some subjects, an intense uptake is seen in the supraclavicular regions, and appear to be colocalized with fat tissue rather than muscle [74–76]. Recently, a large study examined PET/CT scans from 1,972 patients, and found a high signal consistent with BAT activity in the anterior region of the neck and chest in 7.5% of women and 3.1% of men [77]. Biopsies were also taken from 33 patients and showed multilocular and UCP-1 positive cells [77]. Similar histological findings were reported from a smaller study of five healthy subjects, in which the tissue biopsies revealed BAT biomarkers, i.e. DIO2, PGC1a, PRDM16, ADRB3 and mitochondrial protein cytochrome *c* protein [78]. Increased 18F-FDG uptake is highest in the supraclavicular region, but is also present in the areas where BAT have been previously localized [73, 76, 77, 79].

Whether BAT plays a significant role in obesity and the metabolic syndrome is still unresolved. Initial reports suggest that cold-induced glucose uptake is increased in paracervical and supraclavicular adipose tissue in healthy subjects [73, 78], and that BAT activity is positively correlated with resting metabolic rate [73]. BAT activity is also inversely associated with adiposity, at least in healthy men <32 years

old [73, 77]. However, BAT was found most frequently in young women and least frequently in older, overweight men and in patients receiving beta-blockers [77]. The following questions need to be addressed with respect to the importance of BAT in energy balance in humans. Does BAT play a role in adaptive non-shivering thermogenesis in humans? Does BAT expand in response to chronic cold-exposure? A connection between BAT and thermogenesis has been proposed in adult humans who live in cold regions, such as Inuit Eskimo, Athapaskan and Alacaluf Indians, and Norwegian Lapps. In some populations, the basal metabolic rates may increase by 30–40%, allowing people to sleep in ambient temperatures as low as 2–5°C [80]. Another important issue is whether BAT is reduced in obesity, and if so, whether the change in BAT is a cause or consequence of obesity. It seems logical that obesity will result in a shift of energy storage from BAT to WAT. Moreover, obese individuals are better insulated from the cold by WAT, hence BAT is less actively challenged and should become smaller. The answers to these issues could have a significant impact on future therapeutic strategies for obesity, diabetes and other metabolic disorders.

Conclusion

Fuelled by the desire to better understand the association between obesity and the metabolic syndrome, significant strides have been made in our knowledge of the development, structure and function of both WAT and BAT. With this knowledge has come a renewed appreciation of the degree of communication that exists between adipose tissue and various physiological systems. Adipose tissue exhibits remarkable plasticity in its structure and function in obesity, including activation of innate immunity, and alterations in the levels of circulating fatty acids, adipokines, cytokines and other factors. While insulin resistance is a sine qua non of obesity, most patients do not develop diabetes, likely because of adequate compensation by the pancreatic B cell. The advances in our understanding of the molecular regulation of adipose tissue structure and function could provide novel insights into the how adipose tissue signals to itself and other organs, and how dysregulation of these interactions culminates into obesity-related diseases.

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