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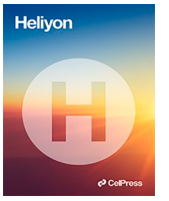

Review article

Regional primary preadipocyte characteristics in humans with obesity and type 2 diabetes mellitus

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ABSTRACT

The excessive accumulation of adipose tissue in obesity appears to result in adipose tissue dysfunction perpetuating the onset of obesity-related diseases, including type 2 diabetes (T2DM). In humans, adipose tissue is stored in several depots including subcutaneous and visceral. These depots contribute to the pathology of obesity differently owing to differences in the tissue microenvironment, a main one being preadipocyte function. In examining adipocyte and preadipocyte characteristics, many have used the 3T3-L1 murine cell lines. Though these cell lines provide valuable mechanistic data, the results remain to be translated to humans. Experiments using primary human preadipocytes has shown that obesity and T2DM impact preadipocyte phenotypes. The objective of this review is to describe the differences in regional characteristics of primary preadipocytes collected from humans with obesity and to discuss how these characteristics might be affected in type 2 diabetes mellitus. In doing so, we will show that the characteristics of regional primary preadipocytes in humans are differentially affected by obesity and the development of T2DM.

1. Introduction

In obesity, the excessive accumulation of adipose tissue appears to result in adipose tissue dysfunction, perpetuating the onset of obesity-related diseases, including type 2 diabetes. Though there are several characteristics that have been shown to be irregular in adipose tissue of individuals with obesity, a main one is preadipocyte function. Preadipocytes are progenitors of adipocytes, comprising ~17–30 % of the stromovascular fraction in subcutaneous adipose tissue [1], and visceral adipose tissue [2,3]. Studies show that preadipocyte characteristics are implicated in type 2 diabetes and may be specific to the depots from which they originate.

In humans, adipose tissue is stored in several depots including subcutaneous and visceral. Though most adipose tissue is stored subcutaneously just beneath the skin, we and others have shown that this depot is not uniform as upper body subcutaneous adipose tissue has different properties than lower body subcutaneous adipose tissue [4,5]. Another well studied compartment of adipose tissue is that stored viscerally around the organs. It is well established that the accumulation of visceral adipose tissue is more strongly associated with obesity-related disorders than subcutaneous adipose tissue. However, both these depots appear to contribute to the

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pathology of obesity in different ways given variations in the tissue microenvironment that includes preadipocytes [6,7].

Preadipocytes can be characterized by specific surface markers [8], protein secretion [9], electrophysiological properties [10], genetic analyses [11] and epigenetics. These cells undergo constant proliferation and differentiation during adipogenesis, which enable the maintenance of functional plasticity and facilitate the expansion of adipose tissue throughout the human lifespan [12]. In general, the number of adipocytes is thought to be determined early in life and remain relatively stable throughout the lifespan. In adulthood, adipose tissue expansion is believed to occur predominantly by hypertrophy [13,14]. However, more recent studies have challenged this paradigm by demonstrating that the generation of new adipocytes from preadipocytes in response to caloric excess [15]. Therefore, preadipocytes play a significant role in the expansion and microenvironment of adipose tissue.

In examining adipocyte and preadipocyte characteristics, many have used the 3T3-L1 cell lines. Though this murine cell line provides valuable mechanistic insight, whether the findings from these studies are functionally conserved in humans is unclear [16]. The technical development of human preadipocyte primary cultures, has shown that environmental, physiological, and metabolic conditions impact preadipocyte phenotypes. These preadipocytes have been shown to retain their characteristics *in vitro* through several passages. Therefore, this technique has enabled the study of human preadipocytes in the context of metabolic diseases including type 2 diabetes (T2DM). The objective of this review is to describe the differences in regional characteristics of primary preadipocytes in obesity and how these characteristics might be affected by type 2 diabetes mellitus, specifically focusing on studies comparing human regional preadipocytes.

2. Preadipocytes: general functions and characteristics

Fibroblast-like progenitor cells restrict themselves to an adipogenic lineage during the “commitment step” [17]. Though the committed preadipocyte does not undergo any morphological changes from its progenitor, the preadipocyte is able to differentiate to mature adipocytes. Preadipocyte differentiation is characterized by phenotypic changes in cell surface antigen expression as cells differentiate from preadipocytes to mature adipocytes.

There remain many unanswered questions in the understanding of preadipocyte properties and characteristics in humans. Recently, a subpopulation of cells in the stromovascular fraction (SVF) were identified using single cell sequencing that were tangential to adipogenesis [18]. These $CD142^{+}$ cells were found to inhibit differentiation in mouse models *in vivo* and were functionally conserved in human adipogenic stem and progenitor cells (ASPCs) *in vitro* [18]. When focusing on isolated primary human preadipocytes, Tchkonia et al. [19] have shown that two subtypes of preadipocytes exist in humans. One subtype has a more extensive replication, differentiation, adipogenic transcription factor expression than the other. This first subtype of preadipocytes is more abundant in abdominal subcutaneous adipose tissue (AbSAT) and mesenteric adipose tissue depots. The second subtype of preadipocytes, more abundant in omental adipose tissue, has greater apoptotic response to TNF-α. The two subtypes of preadipocytes have distinct cell-dynamic and histological properties, and could impact the plasticity of the cell during the development of the adipose tissue [19]. Interestingly, these two subtypes of preadipocytes have been shown to switch between each other. Extending these observations, Vijay et al. [20], have shown that more than two clusters of preadipocytes exist and that some of these clusters vary with regards to pre-adipocyte maturity and may be depot specific.

These preadipocyte clusters appear to exhibit specific cell surface markers. CD34 is the most reported preadipocyte cell marker [12], promoting cell adhesion, migration and differentiation [21]. $CD34^{+}/CD31^{-}$ is the marker of preadipocytes *in vivo* and *in vitro*. Pref1, also known as Dlk1, has also been described as a surface marker of preadipocytes, and plays a major role in the preadipocyte intracellular protein cascade [22]. The expression of Pref1 is decreased during preadipocyte differentiation into mature adipocytes [23]. Platelet-derived growth factor receptor α (PDGFRα), another marker of preadipocytes, is expressed in preadipocytes but is not expressed in mature adipocytes after the differentiation.

The process of differentiation is mainly regulated by peroxisome proliferator-activated receptor (PPAR) γ and CCAAT/enhancer binding protein α (C/EBPα). PPARγ is described at the “master regulator” of adipogenesis [24,25]. PPARγ activates transcription factor C/EBPα and the two work in synergy to fully activate the differentiation process into mature adipocytes [26,27]. During this differentiation, other early differentiation markers such as AP2 and GLUT4 emerge, highlighting the dynamic changes occurring during this process [28].

In addition to these differentiation regulators, the secretome and the expression profile of preadipocytes are complex and not well described. Secreted factors such as leptin, adiponectin, or even some inflammatory cytokines (TNF-α, IL-6, MCP-1, …) have a significant role in adipogenesis. The secretory profiles of these cytokines and adipokines differ between subcutaneous and omental preadipocytes with 122 differentially secreted proteins identified [29], most of which are involved in chemotaxis and inflammation and have been shown to be affected by obesity and T2DM [29].

Indeed, the dysfunction of adipose tissue and the chronic low-grade inflammation that develop with obesity and insulin resistance may directly impact preadipocyte characteristics and adipogenesis. In considering preadipocyte characteristics, the region of origin should be noted since different subtypes of preadipocytes dominate different depots. Fortunately, *in vitro* studies on human primary preadipocyte cultures showed that regional differences are retained for at least 40 cell generations in colonies derived from single cells [15], allowing for a more comprehensive picture in the study of human primary preadipocytes.

3. Proliferation

3.1. Regional differences of primary preadipocyte proliferation in obesity

The number of committed preadipocytes, isolated from both AbSAT and omental adipose tissue do not seem to differ between depots [30,31] but varies between individuals [31]. A few studies reported that omental preadipocytes from both males and females with obesity proliferate slower than those from the AbSAT depot (Table 1; Fig. 1) [32,33]. Though differences are observed in proliferation of omental and AbSAT preadipocytes in individuals with obesity, whether they exist between subcutaneous adipose tissue regions is unclear. Tchoukalova et al. [34], found equivalent proliferative capacities between AbSAT and gluteo-femoral subcutaneous preadipocytes from lean and healthy males and pre-menopausal females (18–49 years) (Table 1). However, White et al. [35], showed that in individuals with obesity, gluteo-femoral subcutaneous preadipocytes had greater proliferative capacity compared to AbSAT preadipocytes ($\Delta = 3.224$ percentage point) (Table 1; Fig. 1). These studies show that in a context of obesity, regional preadipocytes are altered, impacting their capacity of proliferation depending on the adipose tissue depots of origin. Though regional differences in preadipocyte proliferation exist, further studies are needed to better understand how these differences may impact adipogenesis in humans with obesity.

3.2. Regional differences of primary preadipocyte proliferation in T2DM

Very few studies have examined the proliferation of regional preadipocytes in T2DM. These studies show that, compared to in obesity, in T2DM there appears to be an overall decrease in preadipocyte proliferation and that the proliferation of preadipocytes is different between regions (Fig. 1). According to Muir et al. [36], the proliferation (% SVF cells) of omental was lower than AbSAT preadipocytes, especially in those with T2DM rather than obesity alone (Table 1). Another study showed no differences in AbSAT preadipocyte proliferation between those with obesity and those with insulin resistance/T2DM (Table 1) [37]. The lower proportion (%SVF cells) of omental preadipocytes described in these studies may contribute to the greater adipocyte hypertrophy and inflammation often observed in the omental adipose tissue depot, characteristics that are often associated with the development of T2DM and insulin resistance [38]. Lower proliferation in omental preadipocytes, in context of T2DM, may contribute to the greater adipocyte hypertrophy and inflammation commonly described in omental adipose tissue.

4. Differentiation

4.1. Regional differences of primary preadipocyte differentiation in obesity

The majority of studies, using oil red O (ORO) staining to examine differentiation, reveal delayed differentiation in omental preadipocytes compared to mesenteric and AbSAT preadipocytes in males and females with obesity (Table 2; Fig. 2) [19,39–45]. This finding is consistent with other studies that have found lower *PPARG* and *C/EBPα* mRNA expression in omental compared to AbSAT preadipocytes (Table 2) [39–41,46–49]. The mRNA expression of PPARG:GAPDH, *PPARG2:GAPDH*, and *PPARG2:G1* was also downregulated in omental compared to AbSAT preadipocytes [50].

The reasons behind differences in differentiation between omental and subcutaneous depots are not well understood. Tchkonia et al. [40] proposed that the slower differentiation of omental preadipocytes could be attributed to their longer telomeres. Impaired adipogenic capacity and differentiation of omental preadipocytes may indicate an earlier induction of AbSAT dysfunction via greater accumulation of *de novo* lipid droplets in AbSAT vs omental adipose tissue [8]. Moreover, impaired adipogenic capacity in omental preadipocytes may lead to adipocyte hypertrophy and increased inflammation in omental adipose tissue.

4.2. Regional differences of primary preadipocyte differentiation in T2DM

In T2DM, differentiation of regional primary preadipocytes from middle-aged humans has been poorly studied. With T2DM there appears to be a delay in human primary preadipocyte differentiation without any significant depot differences (Table 3; Fig. 2) [33,

Table 1
Regional primary preadipocytes proliferation differences and impact of T2DM.

	References	Sex	Age (Range or Mean ± SD)	Regional differences	Differences T2DM vs. Obesity
Lean	Tchoukalova et al. [15]	F/M	26–61	GF = AbSAT	
Obesity	Van Harmelen et al. [32]	F/M	17–61	OM < AbSAT	
	White et al. [35]	F	18–40	GF > AbSAT	
Obesity + T2DM	Muir et al. [36]	F/M	44.5	OM < AbSAT	OM: T2DM < Obesity AbSAT: T2DM = Obesity
	Muir et al. [37]	F/M	40	N/A	AbSAT: T2DM = Obesity
	Sánchez-Ceinos et al. [33]	F/M	44 ± 2	OM < AbSAT	OM: T2DM < Obesity AbSAT: T2DM < Obesity

AbSAT: abdominal subcutaneous, F: female, GF: gluteo-femoral subcutaneous, M: male, OM: omental, T2DM: type 2 diabetes.

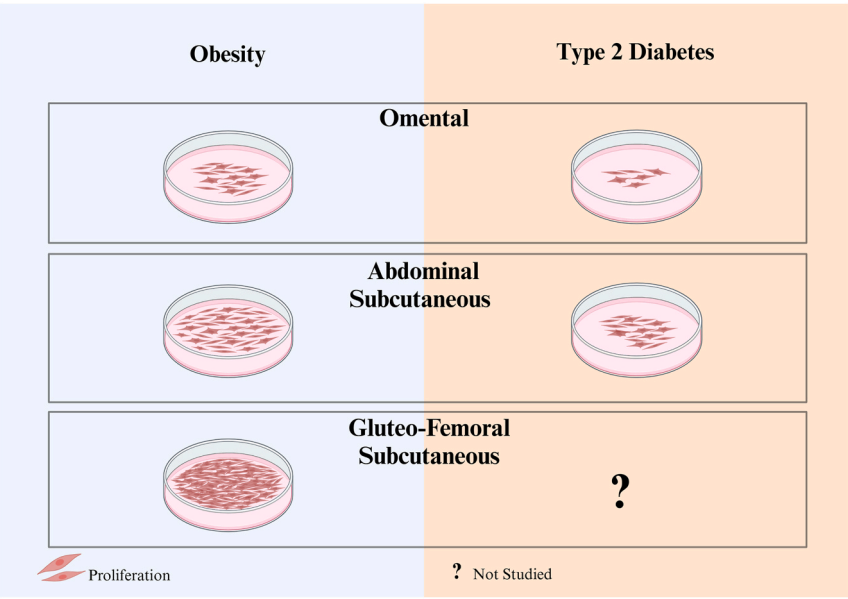

Fig. 1. Representation of proliferative capacity in regional primary preadipocytes from individuals with obesity and type 2 diabetes. In obesity, omental primary preadipocyte proliferation is decreased compared to abdominal and gluteo-femoral subcutaneous preadipocytes. Moreover, the proliferative capacity of gluteo-femoral subcutaneous primary preadipocytes is greater than abdominal subcutaneous preadipocytes. With T2DM, the proliferation in both omental and abdominal subcutaneous preadipocytes is decreased compared to those with obesity only. A significant regional difference in proliferation is reported between omental and abdominal subcutaneous preadipocytes in individuals with T2DM, with decreased proliferation in omental primary preadipocytes. The proliferation of gluteo-femoral subcutaneous primary preadipocytes from humans with T2DM has not yet been studied.

Table 2
Regional primary preadipocytes differentiation differences in obesity.

References	Sex	Age (y) (Range or mean ± SD)	Measurement of differentiation	Regional differences
Sewter et al. [50]	F/M	38–64	mRNA expression of PPARG/GAPDH, PPARG2/GAPDH, and PPARG2/g1	OM < AbSAT
Tchkonia et al. [39]	F/M	29–61	ORO, G3PDH activity, mRNA expression PPARG and C/EBPα	OM < AbSAT
Tomlinson et al. [47]	F	28–65	mRNA expression PPARG and C/EBPα	OM < AbSAT
Van Harmelen et al. [51]	F/M	22–65	ORO, G3PDH activity	OM = AbSAT
Van Harmelen et al. [32]	F/M	17–61	ORO, G3PDH activity	OM = AbSAT
Tchkonia et al. [40]	F	18–69	ORO, G3PDH activity, mRNA expression PPARG and C/EBPα	OM < AbSAT
Tchkonia et al. [46]	F/M	38.8 ± 3.0	ORO, G3PDH activity, mRNA expression PPARG and C/EBPα	OM < AbSAT
Blouin et al. [41]	F	41–58	ORO, G3PDH activity, mRNA expression PPARG and C/EBPα	OM < AbSAT
Dicker et al. [42]	F	40 ± 7	ORO, G3PDH activity	OM < AbSAT
Tian et al. [43]	F	32.19 ± 7.03	ORO, G3PDH activity	OM < AbSAT
Hurtado del Pozo et al. [48]	F/M	41.1 ± 5.5	mRNA expression PPARG and C/EBPα	OM < AbSAT
Lessard et al. [44]	F	35–58	ORO, G3PDH activity	OM < AbSAT
Michaud et al. [49]	F	37–54	mRNA expression PPARG and C/EBPα	OM < AbSAT
Liu et al. [45]	F/M	49.3 ± 8.7	ORO, G3PDH activity	OM < AbSAT

AbSAT: abdominal subcutaneous, F: female; M: male OM: omental, ORO: Oil Red O staining; listed by year.

52]. Jaganjac et al. [53] observed that, compared to those with obesity, those with insulin resistance and T2DM had a more than 2-fold decrease in the differentiative capacity of omental preadipocytes. Sánchez-Ceinos et al. [33], also reported lower *PPARG* mRNA expression in omental preadipocytes with insulin resistance compared to with obesity alone. In contrast, Andersen et al. [54] did not find any difference in omental differentiation from males with T2DM compared to males with obesity. With regards to AbSAT preadipocytes, a downregulation of *PPARG, C/EBPα* in males and females was also observed with insulin resistance and T2DM compared to in obesity [55]. Lower preadipocyte differentiation in omental and AbSAT is significant because, independent of BMI, delayed

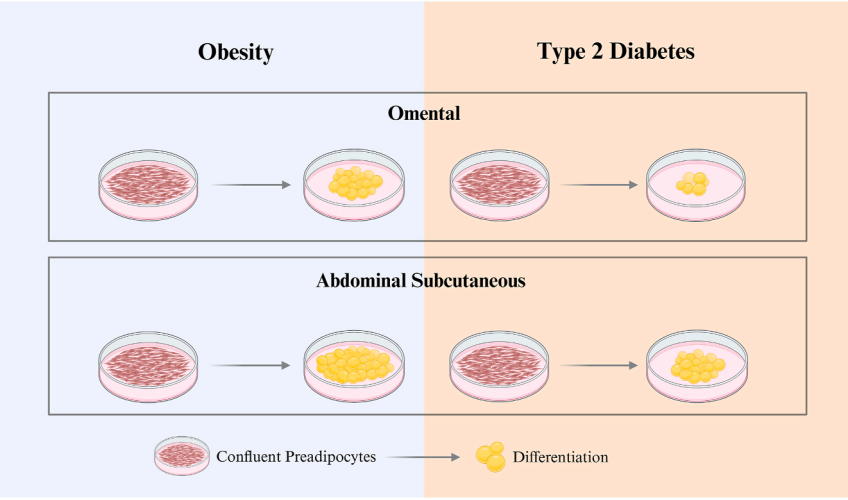

Fig. 2. Representation of differentiative capacity of regional primary preadipocytes from individuals with obesity and type 2 diabetes. In obesity, omental primary preadipocyte differentiation is delayed compared to abdominal subcutaneous preadipocytes. With T2DM, the differentiation in both omental and abdominal subcutaneous preadipocytes is decreased compared to those with obesity only. A significant regional difference in differentiation is observed in T2DM, with a decreased differentiation in omental vs abdominal subcutaneous primary preadipocytes.

Table 3
Differences in differentiation of regional primary preadipocyte in obesity and T2DM.

References	Sex	Age (Range or mean ± SD)	Measurement of differentiation	Differences T2DM vs. Obesity
Van Tienen et al. [55]	F/M	52 ± 12	mRNA expression of PPARG, C/EBPα	AbSAT: T2DM < Obesity
Almuraikhy et al. [52]	F/M	36	Lipidtox positive, mRNA expression PPARG and C/EBPα	AbSAT: T2DM < Obesity
Jaganjac et al. [53]	F/M	35	Lipidtox positive	OM: T2DM < Obesity
Andersen et al. [54]	M	26–55	mRNA expression of PPARG	OM: T2DM < Obesity
Sánchez-Ceinos et al. [33]	F/M	44 ± 2	PPARG, FABP4, and ADIPOQ	OM: T2DM < Obesity AbSAT: T2DM < Obesity

AbSAT: abdominal subcutaneous, F: female, M: male, OM: omental, T2DM: type 2 diabetes; listed by year.

differentiation is associated with insulin resistance [33,45]. In obesity, the differentiation of omental preadipocytes is already delayed compared to that of AbSAT preadipocytes. T2DM appears to exacerbate this delay, resulting in even slower differentiation of omental preadipocytes than in obesity alone. The differentiation of omental preadipocytes may play a significant role in the development of T2DM and insulin resistance.

Oppositely, medications (i.e. thiazolidinediones (TZDs)) that promote differentiation have been successfully used in the management and treatment of T2DM. TZD class medications exert their mechanism of action as PPARγ agonists. Though TZDs enhance differentiation in both depots, omental preadipocytes are not as responsive to the agonistic effects of TZDs compared to AbSAT preadipocytes [56]. Exposure of AbSAT preadipocytes to TZDs induces a greater and complete differentiation [57]. These findings underscore the alteration of the differentiation process in T2DM and the importance of preadipocyte differentiation in adipose tissue to glucose homeostasis.

5. Expression profile

5.1. Regional differences of primary preadipocyte expression profiles in obesity

5.1.1. Inflammation-related gene expression profile

The few studies that have analysed differences in regional human primary preadipocytes, have mostly found differences in expression profiles between depots in individuals with obesity. However, the extent and direction of these differences remains unclear. Indeed, with obesity, upregulation and higher mRNA levels of *IL-6, IL-8,* and *MCP*-1 mRNA expression in omental preadipocytes were reported, while this upregulation was not observed in AbSAT preadipocytes (Fig. 3) [29,58]. Less examined markers of inflammation, *WNT5A* and *RARRES2* mRNA, have been also investigated in the context of depot differences. In omental preadipocytes, the mRNA expression of *WNT5A* was reported to be 15-fold greater compared to AbSAT preadipocytes [58]. *RARRES2*, which codes for the proinflammatory adipokine chemerin, was also upregulated in obesity by almost 3-fold in omental preadipocytes but not in AbSAT preadipocytes [29]. Collectively, these data suggest that omental preadipocytes contribute to the pro-inflammatory state in obesity to a greater extent than AbSAT preadipocytes.

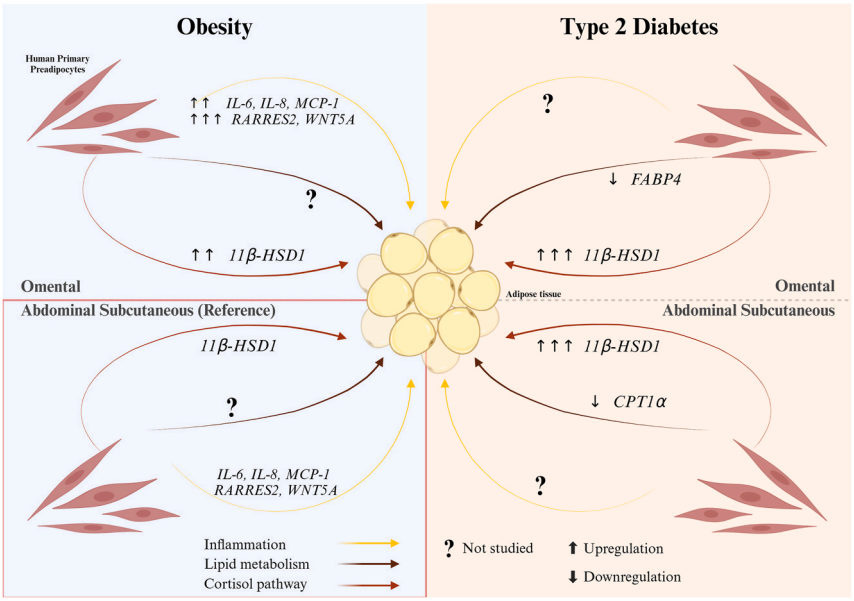

Fig. 3. Changes in expression profiles of regional primary preadipocyteswith type 2 diabetes relative to those from obese a abdominal subcutaneous depots. In obesity, the mRNA expression levels in inflammation (yellow arrow) and cortisol pathway-related genes (red arrow) are increased in omental compared to abdominal subcutaneous preadipocytes. With T2DM, the expression levels of some lipid metabolism-related genes (brown arrow), such as *FABP4* and *CPT1α,* are decreased compared to reference preadipocytes. However, in T2DM, 11β-HSD1 expression, a major gene in the cortisol pathway contributing to central obesity, is increased in both depots compared to preadipocytes in those with obesity only. 11β-HSD1: 11β-hydroxysteroid dehydrogenase type 1, CPT1α: carnitine palmitoyl transferase A1, FABP4: fatty acid binding protein 4, IL: interleukin, RARRES2: retinoic acid receptor responder 2, WNT5A: Wnt Family Member 5A

5.1.2. Lipid metabolism-related gene expression profile

There are currently no studies reporting the effect of obesity on lipid metabolism-related gene expression profiles of regional primary preadipocytes in humans. However, differences between regional primary preadipocytes from lean, healthy individuals has been shown. In 2011, Moreno-Navarrete et al. [59] reported that in lean omental and AbSAT preadipocytes, the relative gene expression of fatty acid synthase (FASN) and fatty acid binding protein 4 (FABP4) was upregulated during differentiation. The upregulation of these genes was, however, diminished in omental compared to AbSAT preadipocytes. The same study also showed that the gene expression of acetyl-CoA carboxylase (ACC) was upregulated in both omental and AbSAT preadipocytes. In contrast with *FASN* and *FABP4*, no regional differences between adipose tissue depots were observed [59]. The diminished upregulation of *FASN* and *FABP4* in omental preadipocytes from healthy individuals could suggest that these genes are involved in the delayed differentiation observed in obesity in omental preadipocytes.

5.1.3. Cortisol pathway-related gene expression profile

Differences in gene expression involved in the cortisol pathways have also been reported in regional primary preadipocytes in context of obesity. The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), also known as cortisone reductase, is responsible for converting cortisone to cortisol and vice versa. Visceral adipose tissue exhibits elevated levels of 11β-HSD1, contributing to central obesity. Within adipose tissue, 11β-HSD1 is implicated in the upregulation of both adipocyte differentiation and preadipocyte proliferation [47]. The expression of 11β-HSD1 varies between regional primary preadipocytes from lean individuals to those with obesity. According to Bujalska et al. [60], omental preadipocytes from individuals with obesity had much greater *11β-HSD1* gene expression than those from lean middle-aged females. In contrast, in AbSAT preadipocytes, the mRNA levels of *11β-HSD1* were similar between males and females who are lean and those with obesity [47,60,61]. *11β-HSD1* expression appears to be specifically associated with central obesity, as the upregulation of this gene is observed in omental preadipocytes only.

In conclusion, the expression profiles of regional primary preadipocytes are complex and not well studied and described at present. It is evident that obesity negatively affects the expression profile of primary preadipocytes in a region-specific manner (Fig. 3). The observed regional differences in mRNA gene expression highlight the specificity of each adipose tissue depot in the context of obesity. However, these studies are limited in that only mRNA expression is considered. The expression level of mRNA is an indicator but does not predict into protein content [62]. The relationship between mRNA expression and protein content is influenced by spatial and temporal variations, and the local resources availability for protein synthesis [63]. Further studies are required to determine how these differences in mRNA expression affect inflammation within the tissue and at the whole-body level.

5.2. Regional differences of primary preadipocyte expression profiles in T2DM

5.2.1. Inflammation-related gene expression profile

There are currently no studies reporting the effect of T2DM and insulin resistance on the inflammation-related gene expression profile of regional primary preadipocytes in humans.

5.2.2. Lipid metabolism-related gene expression profile

There are very few studies that have examined expression of genes related to lipid metabolism in regional primary preadipocytes in middle-aged (~35–55 years) males and females with T2DM (Fig. 3). These studies show that T2DM negatively alters the expression of these genes, but the extent of these alterations remain poorly described. Compared to individuals with obesity, omental preadipocytes from males and females with T2DM and insulin resistance had lower expression of *FABP4* [33,54]. This downregulation of *FABP4* implies a potentially decreased lipolytic capacity of omental adipose tissue, leading to the described accumulation of visceral adipose tissue and chronic inflammation. Additionally, carnitine palmitoyl transferase A1 (*CPT1α*), a less-studied gene involved in the carnitine-dependant transport of fatty acids across the mitochondria, has been reported to be downregulated in AbSAT preadipocytes in those with insulin resistance and T2DM vs those with obesity only [55]. The downregulation in *CPT1α* may indicate altered β-oxidation in AbSAT in T2DM. These findings suggest that T2DM might disrupt lipid metabolism in regional preadipocytes, contributing especially to omental adipose tissue accumulation and inflammation.

5.2.3. Cortisol pathway-related gene expression profile

There is only one study that examined cortisol pathway-related gene expression in the context of T2DM that could be found. This study compared mRNA expression of *11β-HSD1* and *H6PD*, in both omental and AbSAT primary preadipocytes from males who were overweight with and without T2DM [64]. The investigators did not find any variations between adipose tissue regions, but they reported an upregulation of *11β-HSD1* and *H6PD* mRNA in males with T2DM compared to those without T2DM (Fig. 3) [64]. The failure to downregulate 11β-HSD1 activity in patients with T2DM may indicate a propensity towards central adiposity, contributing to the pathogenesis of T2DM.

T2DM significantly alters the gene expression profiles in regional primary preadipocytes, particularly in the lipid metabolism and cortisol pathway (Fig. 3). However, further studies are needed to understand the differences in gene expression profiles between adipose tissue depots and their role in the development of T2DM. These findings emphasize the need to understand the complex molecular mechanisms and their changes with T2DM.

6. Conclusion

In this review, we have summarized the regional characteristics of primary preadipocytes in human obesity and T2DM. Though primary preadipocytes from visceral and subcutaneous adipose tissue depots have some common characteristics, they also differ depending on the depot of origin. Our findings suggest that *in vitro* cultures of primary preadipocytes from individuals with obesity and T2DM present regional disparities in proliferation, differentiation, and expression profiles. Specifically, in obesity, omental primary preadipocytes exhibit delayed proliferation and differentiation compared to those from abdominal and gluteo-femoral subcutaneous regions. Moreover, the expression profile of obese omental primary preadipocytes appears to be more pro-inflammatory and display altered lipid metabolism compared to AbSAT preadipocytes. Although omental adipose tissue shows higher levels of inflammation, the larger volume of subcutaneous adipose tissue implies that inflammation in this depot could be a more important factor in chronic low-grade inflammation. The differences between regional primary preadipocytes suggest specific mechanisms in adipose tissue dysfunction, highlighting diverse states and distinct roles of regional adipose tissue in obesity-related dysfunction. Nevertheless, it remains uncertain whether adipose tissue becomes dysfunctional prior to disease onset or whether presence of metabolic disease affects adipose tissue dysfunction, and how each adipose tissue depot contributes to obesity development. Furthermore, our review provides evidence that regional primary preadipocytes in humans are uniquely and negatively affected by insulin resistance and T2DM. In T2DM, omental preadipocyte proliferation is delayed, and differentiation capacity reduced compared to obesity. While inflammatory genes expression or protein levels studies are lacking, T2DM appears to negatively impact genes associated with lipid metabolism and the cortisol pathway, potentially contributing to central obesity.

Understanding the role of regional primary preadipocytes in adipogenesis within the context of these pathologies is crucial for the development of targeted prevention and treatment strategies. In conclusion, our study highlights the importance of investigating regional differences in adipose tissue and calls for further research to explore the characteristics of preadipocytes and adipose tissue and how these characteristics contribute towards the evolution of metabolic disease.

7. Clinical perspectives

In the context of obesity, it is well-established that visceral adipose tissue is associated with an elevated risk of developing T2DM. However, precise mechanisms underlying regional adipose tissue dysfunction remain poorly understood. Preadipocytes, precursors to adipocytes, are key to adipose tissue expansion and dysfunction in obesity and T2DM. Understanding the function of regional primary preadipocytes from individuals with obesity and T2DM, could significantly enhance our comprehension of how the development of T2DM is linked to adipose tissue dysfunction. This knowledge could enable the development of targeted therapies for this disease.

CRediT authorship contribution statement

Claire Plissonneau: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Sylvia Santosa:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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