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REVIEW

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Transcriptional and epigenetic control of adipocyte remodeling during obesity

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Abstract

The rising prevalence of obesity over the past decades coincides with the rising awareness that a detailed understanding of both adipose tissue biology and obesity-associated remodeling is crucial for developing therapeutic and preventive strategies. Substantial progress has been made in identifying the signaling pathways and transcriptional networks that orchestrate alterations of adipocyte gene expression linked to diverse phenotypes. Owing to recent advances in epigenomics, we also gained a better appreciation for the fact that different environmental cues can epigenetically reprogram adipocyte fate and function, mainly by altering DNA methylation and histone modification patterns. Intriguingly, it appears that transcription factors and chromatin-modifying coregulator complexes are the key regulatory components that coordinate both signaling-induced transcriptional and epigenetic alterations in adipocytes. In this review, we summarize and discuss current molecular insights into how these alterations and the involved regulatory components trigger adipogenesis and adipose tissue remodeling in response to energy surplus.

INTRODUCTION

Obesity is a complex and multifactorial metabolic disease, the prevalence of which has exponentially increased in the past 30 years. In 2016, the World Health Organization estimated that more than 1.9 billion people worldwide were overweight, among whom more than 650 million people had obesity (1). This pathological condition is currently one of the major challenges for health care systems, as it represents a major risk factor for the development of comorbidities such as diabetes, cardiovascular disease, hypertension, dyslipidemia, coronary heart disease, and certain types of cancer (2). Obesity is characterized by excess body fat accumulation, an outcome of the imbalance between energy intake and energy expenditure. Although a small number of cases result from monogenic alterations, the common form of obesity is the outcome of a complex interplay of multiple factors (3). This recognition has sparked extensive interest in understanding how an obesogenic environment triggers adipose tissue remodeling and thereby systemically influences metabolic homeostasis. Recent evidence suggests that adipose tissue remodeling cannot be understood without insights into the alterations of the epigenome (epigenetic chromatin modifications) and the transcriptome (gene expression) that occur in the adipocytes in particular (Figure 1). These alterations and their influence on the development and the progression of obesity will likely differ between individuals. Therefore, their study promises to contribute to the development of future personalized therapeutic strategies.

ADIPOSE TISSUE ORGANS

In mammals, the adipose organ is mainly composed of two tissues, the white adipose tissue (WAT) and the brown adipose tissue (BAT). Both consist of a pool of heterogeneous cell types that can be clustered into two main groups, mature adipocytes and the stromal vascular fraction (SVF). The mature adipocytes represent 20% to 30% of total cells, and the SVF is composed of mesenchymal stem cells, preadipocytes, fibroblasts, endothelial cells, vascular progenitors, and immune cells, including macrophages, T cells, and B cells (4). WAT is characterized by white adipocytes containing unilocular lipid droplets and it has an extensive role in the storage and release of

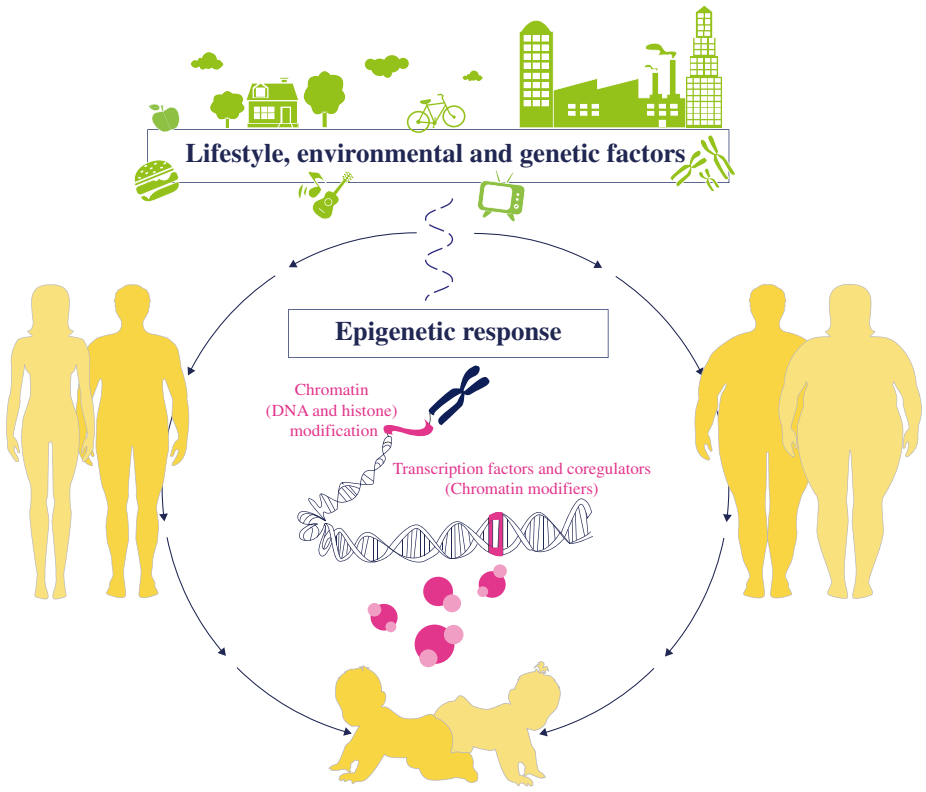

FIGURE 1 Components of epigenetic responses that influence obesity. Lifestyle, environment, and genetics are contributing factors that trigger the imbalance between caloric intake and caloric expenditure. All these factors lead to personalized epigenetic signatures that can influence the progression of obesity and perhaps predispose progeny to develop obesity

free fatty acids (FFAs) upon energetic request of the organism. It is an active endocrine organ that communicates with other metabolically relevant organs by secreting adipokines (5). WAT is classified as visceral fat, surrounding the internal organs in the intra-abdominal cavity, and as subcutaneous fat, located under the epidermis throughout the body (6). The regional distribution of WAT is very important in predicting the complications associated with obesity. Visceral obesity influences insulin sensitivity, glucose tolerance, and lipid metabolism, leading to metabolic syndrome. In contrast, subcutaneous fat serves as a safe harbor for substantial, and potentially toxic, quantities of lipids and it has a positive effect on glucose tolerance (7).

BAT accumulates and stores lipids in multilocular brown adipocytes that contain a large number of mitochondria enriched with the uncoupling protein 1 (UCP1). BAT's main function is to maintain core body temperature in response to cold stress through a process known as thermogenesis, in which UCP1 uncouples oxidative phosphorylation from ATP production to generate heat (8). Evidence shows that, in humans, BAT is not only present in newborns but also in adults above the clavicle and in the subscapular region (9). UCP1-expressing thermogenic adipocytes can also be found in WAT upon prolonged cold stimulation or activation of pathways that increase intracellular cyclic adenosine monophosphate (cAMP). These cells, called "beige" or "brite" adipocytes, have a higher mitochondrial density with a more oxidative phenotype that promotes energy consumption compared with typically nonthermogenic white adipocytes in WAT (10).

PHYSIOLOGICAL FUNCTIONS OF WHITE ADIPOCYTES

The primary function of white adipocytes is to maintain metabolic homeostasis through the storage and release of FFAs. The energy surplus is accumulated in triglyceride-containing lipid droplets through lipogenesis, whereas, upon energy expenditure or starvation, the lipid reserves are released through lipolysis. The balance between lipid influx and efflux into/from the adipocytes is sensitive to nutrition and multiple hormone-sensitive enzymes (11). In the presence of high blood glucose levels, insulin is released from β cells of the pancreas, promoting glucose uptake in adipocytes. Within adipocytes, glucose has different potential destinies (12). It can be metabolized into acetyl coenzyme A (CoA), a substrate for the synthesis of endogenous FFAs through de novo lipogenesis, or, primarily, it is metabolized into glycerol, an important substrate for the esterification of FFAs (12). The FFAs used for triglyceride production in adipocytes come mainly from circulating triglycerides or lipoprotein hydrolyzed by the key enzyme lipoprotein lipase (LPL) and transported into the adipocytes by scavenger receptor CD36 or fatty acid binding proteins (13). Triglyceride synthesis is then achieved by the

sequential actions of multiple enzymes, including diacylglycerol acyltransferase, which plays a critical role in their deposition in lipid droplets (14). Nevertheless, upon metabolic demand, the elevated levels of circulating glucagon and catecholamine (the latter released by the sympathetic nervous system) stimulate the lipolytic process. Once triggered, the cAMP-dependent protein kinase A (PKA) pathway induces the activation of the following lipases: adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (15), which break down triglycerides into individual fatty acids that are released from the adipose tissue for systemic utilization (Figure 2). Insulin has an important role in regulating lipogenesis and lipolysis. It suppresses lipolysis by inactivating the cAMP pathway and preventing ATGL and HSL activation (16). Furthermore, insulin promotes fatty acid uptake and esterification, increasing the expression and activity of LPL and the translocation of fatty acid transport proteins and their related gene expression (17). Interestingly, recent work has identified novel adipocyte functions for the membrane ATP-binding cassette transporter G1 (ABCG1) beyond its well-characterized role in the regulation of cholesterol efflux. ABCG1 seems to be involved in triglyceride storage in adipocytes (18), and it mediates sphingomyelin efflux and contributes to increased LPL activity (19). In addition, it was shown that ABCG1 plays an important role during adipogenesis and, in individuals with obesity, its expression is associated with fat mass formation and BMI (19).

Over the past two decades, it has become evident that adipose tissue also has an endocrine function that includes the production of a variety of factors such as metabolites, lipids, and adipokines (20). Leptin was the first adipokine discovered, followed by adiponectin. Afterwards, many other adipokines were discovered, including resistin and proinflammatory cytokines such as C-C motif chemokine 2 (CCL2, also known as monocyte chemoattractant protein-1 [MCP1]), interleukin 6 (IL-6), and tumor necrosis factor α (TNFα) (20). Interestingly, adipocyte-secreted factors have the ability to regulate diverse biological processes, including metabolism and inflammation, by acting locally as paracrine factors or by acting distally as endocrine factors. Not surprisingly, their dysregulated production or secretion is implicated in metabolic and inflammatory diseases (21). We recently demonstrated that the transcriptional reprogramming of adipose tissue during energy surplus leads to the production of adipokines that influence adipose tissue remodeling and pancreatic islet function (insulin secretion) in the context of obesity and type 2 diabetes (22).

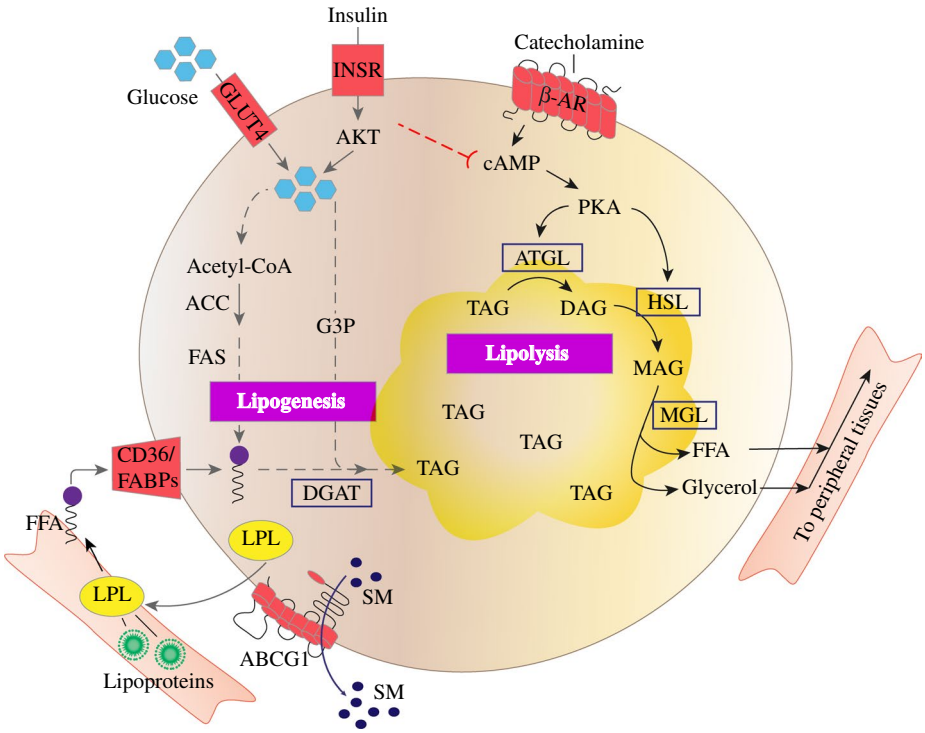

FIGURE 2 Schematic representation of lipogenesis and lipolysis in adipocytes. Lipogenesis is illustrated on the left, whereas lipolysis is illustrated on the right of the figure. In lipogenesis, FFAs from the circulation or generated through de novo lipogenesis are used as substrates for the synthesis of TAGs stored in the lipid droplets. In lipolysis, TAGs are broken down to FFAs and glycerol, which are released in the circulation to peripheral tissues. ABCG1, ATP-binding cassette transporter G1; ACC, acetyl coenzyme A carboxylase; ATGL, adipose triglyceride lipase; β-AR, β-adrenergic receptors; DAG, diacylglycerol; DGAT, diacylglycerol acyltransferase; FABP, fatty acid binding protein; FAS, fatty acid synthase; FFA, free fatty acid; G3P glycerol-3-phospate; GLUT4, glucose transporter type 4; HSL, hormone-sensitive lipase; INSR, insulin receptor; LPL, lipoprotein lipase; MAG, monoacyl glycerol; MGL, monoacylglycerol lipase; SM, sphingomyelin; TAG, triglyceride

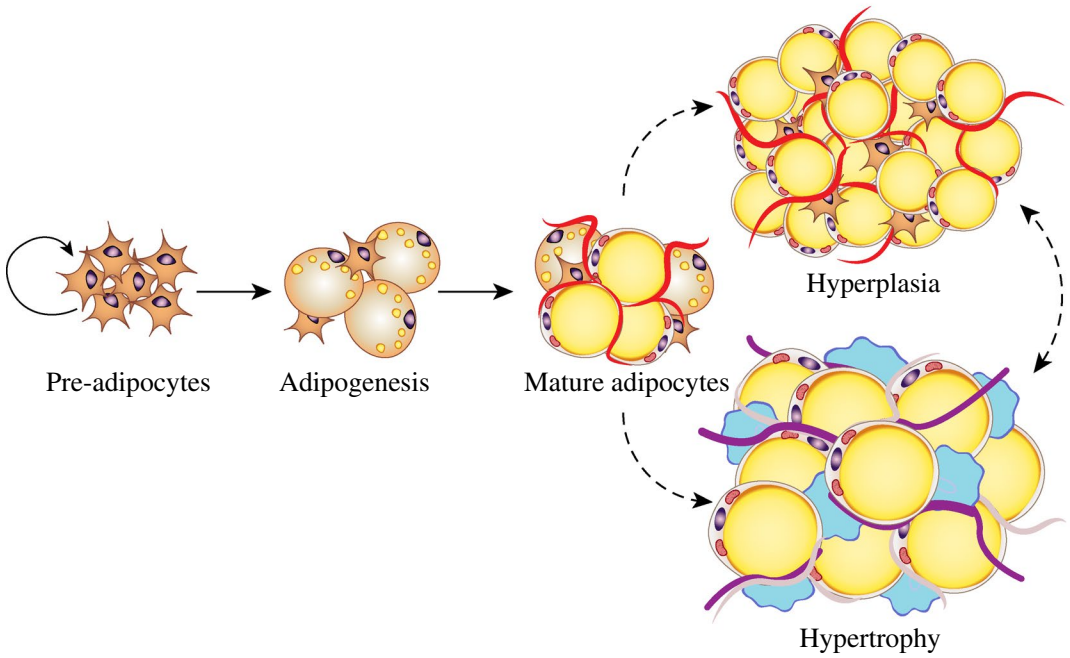

FIGURE 3 Mechanisms of adipose tissue remodeling. Adipose tissue expansion is achieved through proliferation of tissue-resident precursors and differentiation in mature adipocytes (hyperplasia), as well as increase of cell size of existing adipocytes (hypertrophy). Hyperplasic adipose tissue is able to maintain proper vascularization, and it is generally considered a healthy adaptation. Hypertrophic adipose tissue is associated with increased hypoxia and inflammation that lead to unhealthy expansion

ADIPOSE TISSUE REMODELING: HYPERPLASIA VERSUS HYPERTROPHY

Fat mass remodeling is an adaptive response of adipocytes to the body's energetic demand. In order to maintain metabolic homeostasis, adipocytes release FFAs during times of energy request and safely store the lipid excess during overnutrition, preventing lipotoxicity and lipid accumulation in ectopic places such as liver, bone marrow, and skeletal muscle (6). Adipose tissue expansion in adulthood is achieved mainly by two processes: hypertrophy, increasing lipid accumulation and size of existing adipocytes, and hyperplasia, the proliferation and differentiation of adipocyte precursors to produce new adipocytes, in a process known as adipogenesis. Adipose tissue expansion occurs in combination with remodeling of the extracellular matrix and vasculature (23). The balance between hypertrophy and hyperplasia has a deep impact on metabolic health, and the molecular regulation of these two expansion modes is still not completely understood. During obesity, fat mass is markedly increased, but studies in rodents and humans show that adipocyte expansion proceeds until a given critical volume (24), limiting WAT expansion. Therefore, the increase in cell number must accompany adipocyte hypertrophy in order to achieve excessive fat mass accumulation (Figure 3) (25).

Hypertrophy (the increase of adipocyte size) is considered a maladaptive mechanism of adipose tissue enlargement that induces adipocyte dysfunction and represents a risk factor for developing type 2 diabetes (26). The massive expansion of adipocyte size limits its oxygen diffusion, increasing hypoxia. The transcription factor hypoxia-inducible factor 1α (HIF1α) acts as an oxygen sensor and it is activated in hypoxic conditions (27). The activation of HIF1α induces the expression of profibrotic genes, leading to tissue fibrosis (28). Interestingly, a recent study demonstrated that the inhibition of HIF1α in a specific population of adipose tissue precursor cells promotes adipogenesis and healthy adipose tissue remodeling during obesity (29). Furthermore, hypertrophic adipocytes experience increased mechanical stress from the contact with neighboring cells that contributes, with the hypoxic stress, to adipose tissue inflammation. Hypertrophic adipocytes markedly express proinflammatory cytokines such as CCL2, IL-6, and TNFα (30). In addition, local adipose tissue hypoxia induces a significant change in adipokine production, reducing the secretion of leptin and adiponectin (31). Finally, hypertrophic adipocytes show an increased basal rate of lipolysis, resulting in an overflow of FFAs and cholesterol to muscle and liver, which can cause lipotoxicity (32). In this context, the regional distribution and contribution to leakage of FFAs and cholesterol of the different fat pads are very important. It has been shown that adipocytes from visceral fat have more pronounced lipolytic activity compared with those from subcutaneous depots (33). Additionally, adipocytes derived from omental adipose tissue of individuals with obesity have a higher release of FFAs in response to β-adrenergic stimulation compared with control individuals (34). FFAs released from visceral fat have direct access to the liver through the hepatic portal system, causing several metabolic disturbances such as impaired insulin metabolism and action, increased gluconeogenesis, and release of glucose and altered lipoprotein profiles (2). Reduced hepatic clearance of insulin triggers hyperinsulinemia that causes

downregulation of insulin receptors in skeletal muscle and reduction of glucose uptake. At the same time, pancreatic β cells produce more insulin to reduce glycemia but, over time, their degeneration leads to development of hyperglycemia and onset of type 2 diabetes (2). Hyperplasia (the increase of adipocyte number) is considered a healthier adaptation mechanism of adipose tissue, characterized by smaller adipocytes, that is able to maintain proper vascularization and levels of beneficial adipokines such as leptin and adiponectin (35,36). Interestingly, several cohort studies have demonstrated that hyperplastic remodeling of adipose tissue is correlated with a better metabolic profile in individuals with obesity. For instance, certain people with obesity, called metabolically healthy individuals with obesity, have BMI above 30 kg/m^2 but do not show signs of insulin resistance or dyslipidemia (37). The evident feature of these metabolically healthy individuals with obesity is a higher number of small adipocytes in adipose tissue compared with metabolically unhealthy individuals with obesity (38). Moreover, there are several mouse models showing that genetic induction of de novo adipocyte formation ameliorated insulin resistance and enhanced beneficial storage of fat in adipose tissue of obese mice (39). Pharmacological treatment with thiazolidinediones, targeting peroxisome proliferator-activated receptor γ (PPARγ, the master regulator of adipogenesis), promotes adipogenesis and improves insulin-dependent glucose uptake (40). These findings suggest that promoting hyperplasia and reducing hypertrophy can have a beneficial effect concerning obesity-associated comorbidities.

The storage of excess energy in the adipose tissue is associated with the activation of inflammatory genes and the increased secretion of chemokines that attract immune cells within adipose tissue. In mice, manipulation of the chemotactic MCP1/C-C chemokine receptor type2 system affects macrophage recruitment and/or proliferation in some, but not all, models. These observations leave the pathophysiological relevance of CCL2 in promoting adipose tissue inflammation open to debate. Adipose tissue macrophage (ATM) number significantly correlates with adipocyte size and body mass in obese mice and humans with obesity. Extensive studies have focused on defining the identity and phenotype of these cells under both the lean and obese conditions. Based on the expression of the macrophage (M)1 marker CD11c and the M2 marker CD206 mannose receptor, it has been suggested that a switch from an anti-inflammatory M2 phenotype to a proinflammatory M1 activation state was occurring during weight gain (41). Therefore, macrophages are the major source of innate inflammatory factors, including IL-1β and TNFα in visceral adipose tissue during obesity. Indeed, selective ablation of CD11c$^+$ cells leads to a decrease in adipose and systemic inflammation during high-fat feeding (42). However, more studies have highlighted the heterogeneity and plasticity of ATM phenotypes, further demonstrating that the M1/M2 paradigm may not be applicable *in vivo*. Single-cell transcriptomic approaches confirm the heterogeneity of ATMs, identifying different macrophage populations in obese adipose tissue (43-45). The proinflammatory subset of lipid-laden macrophages in crown-like structures is characterized by the expression of CD9 (46). More recently, Jaitin and colleagues confirmed the phenotype and presence of CD9$^+$ lipid-laden macrophages at crown-like structures. They reported that CD9$^+$ cells counteract inflammation and adipocyte hypertrophy via the triggering lipid receptor expressed on TREM2 (triggering receptor expressed on myeloid cells 2) (43). Proteomics analyses also identified specific ATM markers induced by stimuli reproducing the adipose tissue microenvironment with palmitate, insulin, and high levels of glucose (47). Such activation of ATMs gives rise to the metabolically activated macrophage, which is functionally and phenotypically distinct from classically activated M1 macrophages.

ADIPOSE TISSUE DEVELOPMENT: TRANSCRIPTIONAL NETWORKS GOVERNING ADIPOCYTE COMMITMENT AND DIFFERENTIATION

In humans, subcutaneous WAT develops from weeks 14 to 24 of fetal gestation, and, by week 28, the principal fat deposit areas are organized (48). During the first year of life, the number and size of adipocytes increase, after which the adipocyte number remains stable until adolescence when it appears to increase once again (49). In contrast, the visceral WAT is preferentially formed after birth, and its total amount remains small until adolescence. The embryonic stage in which BAT appears in humans is still unknown, but it can be detected from birth to adulthood (50). It was shown that, although the number of adipocytes is set during childhood and adolescence, 10% of the adipocytes in the WAT of adults underwent annual turnover (51); therefore, adipogenesis must take place to maintain adipose tissue integrity. Human studies correlating fat mass and cell number have demonstrated that, during overfeeding, the number of adipocytes within the adipose tissue increases in adults (52), whereas weight loss has no effect on adipocyte number but is associated with reduction of adipocyte size (51). Interestingly, lineage-tracing studies have demonstrated that white adipocyte precursors derive preferentially from the myogenic factor 5 (MYF5)$^-$ lineage. However, the presence of MYF5$^+$ adipocyte precursors in WAT revealed that white adipocytes can derive from both MYF5$^+$ and MYF5$^-$ lineages (53). BAT adipocyte precursors are derived only from the MYF5$^+$ lineage (54). Both brown and white mature adipocytes can also originate from endothelial precursors (55), whereas brown mature adipocytes can additionally originate from stem cell-like skeletal muscle satellite cells (56). Beige adipocytes can originate either from WAT adipocyte precursors or directly from transdifferentiation of mature white adipocytes (57).

Adipogenesis, the process by which new mature adipocytes are generated from precursor cells, has been intensely studied. Adipocytes arise from pluripotent mesenchymal precursors that have the ability to differentiate into several cell types, including adipocytes, chondrocytes, osteocytes, and myocytes. These progenitor cells are present in the SVF) of adipose tissue as well as in bone marrow. Recent technological advances in flow cytometry and in the generation of transgenic mice have made it possible to isolate

subpopulations in the SVF of WAT that have adipogenic potential. It was demonstrated that adipogenic precursors exhibit unique cell surface markers ($CD29^+$, $CD34^+$, stem cells antigen-1 $[Sca1]^+$, and $CD24^+$), and they have the ability to restore normal WAT in A-Zip lipodystrophic mice (58). Lineage-tracing studies, using genetically marked PPARγ-expressing cells, have identified that adipogenic precursor cells resident in endothelial adipose vasculature may provide signals for adipocyte development (59). Furthermore, a newly discovered subpopulation in the SVF of subcutaneous adipose tissue, characterized by high CD124 and ABCG1 expression, was demonstrated to negatively regulate adipogenesis in a paracrine manner (60). This could indicate that adipocyte differentiation from progenitor cells is influenced by their cross talk with various other cell types. Consistent with this, it was shown that impaired angiogenesis and depletion of adipose-resident macrophages resulted in defective adipose tissue development (61). Remarkably, another single-cell RNA-sequencing study of adipose tissue has identified a rare subpopulation that regulates the thermogenic capacity of neighboring adipocytes (45), thus representing a potential target to increase the oxidative capacity of adipose tissue.

Despite advances in tracing subpopulations that have adipogenic potential *in vivo*, much of what we know about the factors that regulate adipogenesis has often been limited to *in vitro* models using adipogenic cell lines. In this context, adipogenesis can be considered a two-step process: commitment and then terminal differentiation. Under appropriate stimulation, the fibroblast-like progenitor cells become committed to the adipocyte lineage without any morphological changes, giving rise to adipocyte precursors. When induced, these preadipocytes undergo multiple rounds of mitosis (mitotic clonal expansion) and then accumulate triglycerides and differentiate into functional insulin-responsive mature adipocytes. The commitment from pluripotent stem cells to the adipocyte lineage is a complex process that requires the coordinated actions of multiple factors, including insulin, glucocorticoids, transforming growth factor β (TGFβ) superfamily members, including TGFβ itself and bone morphogenetic proteins (BMPs), and wingless (WNT) family members. Insulin is essential for *in vitro* adipocyte differentiation through the activation of the intracellular insulin-signaling pathway. The binding of insulin to the insulin receptors activates a signaling cascade that ultimately enhances the activity of PPARγ and sterol regulatory element-binding protein 1 (SREBP1c) (62). Several studies have demonstrated that disruption of the insulin-signaling pathway leads to failure of adipogenesis (63). Glucocorticoids are also crucial components for adipocyte differentiation. By activating the intracellular glucocorticoid receptor (GR) they facilitate growth arrest and contribute to terminal differentiation by upregulating the expression of CCAAT/enhancer-binding protein (C/EBP) family members (64). Furthermore, glucocorticoids are able to sensitize preadipocytes to the insulin pathway, enhancing the ability of preadipocytes to respond to insulin (65). TGFβ inhibits adipocyte differentiation through the activation of SMAD3 (mothers against decapentaplegic homolog 3), which is able to bind to C/EBPβ and repress its transcriptional activity on the PPARγ promoter (66). Interestingly, SMAD3 can also have a role during the transdifferentiation of mature white adipocytes into brite adipocytes; in fact SMAD3-deficient mice showed increased levels of brite cells in WAT (67). BMPs promote adipocyte differentiation, inducing the phosphorylation and activation of SMAD proteins. The exposure of multipotent stem cells, such as C3H10T1/2, to BMP4 triggers the commitment of these cells to the adipocyte lineage (68). Specifically, BMP4 activates SMAD4 and, consequently, the expression of PPARγ, which promotes adipogenesis (69). Of note, BMP4 also has a function during the terminal phase of differentiation, impairing the acquisition of a brown-like phenotype and inducing a more white-like phenotype of mature adipocytes (70), whereas BMP7 stimulates brown adipogenesis (71). WNT signaling is an important switch in the regulation of adipogenesis. Some WNT family proteins can induce commitment to the adipocyte lineage (72), whereas others can inhibit adipocyte differentiation in the late stages of adipogenesis (73). For example, it was shown that the canonical WNT ligand WNT-10B induced the nuclear translocation of β-catenin and prevented adipocyte differentiation by blocking the expression of PPARγ and C/EBPα (73).

After adipogenic stimulation, committed preadipocytes can become mature adipocytes through the activation of a transcriptional cascade that induces the expression of metabolic genes that characterize mature adipocytes. Although brown and white adipocytes have different embryonic ocrigins and physiological functions, both have similar transcriptional cascades controlling their differentiation into mature adipocytes. Three transcription factor (TF) families (PPARγ; C/EBPα, C/EBPβ, C/EBPδ; and SREBP1c) play a pivotal role in adipogenesis. However, during the first stage of adipogenesis, other TFs have important functions in this process, including GR, signal transducer and activator of transcription 5A, and cyclic AMP-responsive element-binding protein 1 (CREB) (Figure 4). C/EBPβ is rapidly transcribed after the phosphorylation of CREB, induced by cAMP agonists (74), whereas C/EBPβ and C/EBPδ are both induced by activation of GR (75). Although C/EBPβ is rapidly expressed, it remains inactive until 16 hours after induction when it is activated to bind DNA. This is generally concomitant with the entry into the S phase and mitotic clonal expansion. Between 18 and 24 hours post induction, C/EBPβ activates the expression of PPARγ and C/EBPα, which subsequently activate the expression of a larger group of genes that trigger the adipocyte phenotype. Furthermore, PPARγ and C/EBPα positively cross activate each other through their respective C/EBP regulatory elements (76). Once expressed, PPARγ and C/EBPα stimulate SREBP1c, which is involved in the regulation of lipogenesis (77). In addition, specific factors such as PR/SET domain 16 (PRDM16) and PPARγ coactivator 1 α (PGC-1α) are able to drive the thermogenic brown or beige phenotype during adipogenesis (Figure 4). PRDM16 stimulates the expression of brown adipocyte-specific genes and suppresses white adipocyte-specific gene expression. Furthermore, PRDM16 represses the expression of resistin by interacting with the corepressor C-terminal-binding protein 1 and 2, whereas the recruitment of PGC-1α to PRDM16 displaces C-terminal-binding protein, allowing PRDM16 to activate the expression of brown fat genes (78). Interestingly, the interaction

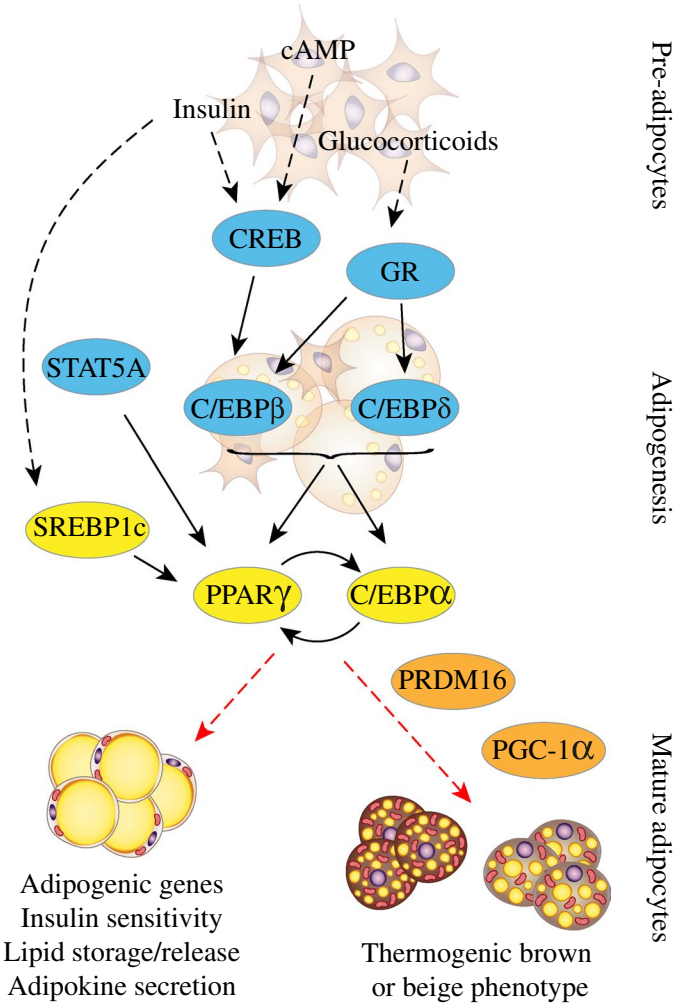

FIGURE 4 The transcriptional cascade controlling adipogenesis. The adipogenic stimuli induce activation of the early adipogenic TFs (blue). These factors orchestrate the subsequent activation of the late adipogenic TFs (yellow), which coordinate to trigger the expression of genes correlated to the adipocyte phenotype. Specific factors (orange) are able to induce the thermogenic brown or beige phenotype. C/EBP, CCAT/enhancer-binding protein; CREB, cAMP-response element binding protein; GR, glucocorticoid receptor; PPARγ, peroxisome proliferator-activated receptor γ; PGC-1α, PPARγ coactivator 1 α; PRDM16, PR/SET domain 16; SREBP1c, sterol regulatory element-binding protein 1; STAT5A, signal transducer and activator of transcription 5A; TF, transcription factor

of PRDM16 with C/EBPβ leads to brown-fated adipocytes in myoblastic precursors (79). PGC-1α acts as a coactivator of PPARγ on the UCP1 promoter, promoting its expression in response to cold exposure (80). The induction of these two regulators may promote an improved metabolic profile of WAT.

EPIGENETIC REGULATION OF ADIPOSE TISSUE REMODELING

There is emerging evidence that epigenetic mechanisms play a crucial role in the regulation of adipose tissue development and remodeling. Since the original introduction, the definition of epigenetics has been repeatedly modified, and, today, epigenetics is more broadly understood as the study of mitotically and/or meiotically heritable phenotype changes without alterations in the DNA sequence itself (81). Dynamic gene expression, termed as the transcriptome, is important during development as well as cell and tissue homeostasis and disease and it can be modulated by several regulatory components. Gene activation is associated with a locally accessible chromatin form, referred to as euchromatin, whereas highly condensed genetic material, known as heterochromatin, is associated with gene repression and silencing. Gene expression can be controlled by covalent DNA methylation or by posttranslational modification of histone tails, including acetylation and methylation. The chromatin modification status, termed as the epigenome, is critical for the creation of the local chromatin environment that induces or represses gene expression. The transcriptome can be directly regulated by epigenetic modification at cis-regulatory elements such as promoters, defined as proximal TF-binding regions close (<2 kilobases [kb]) to the

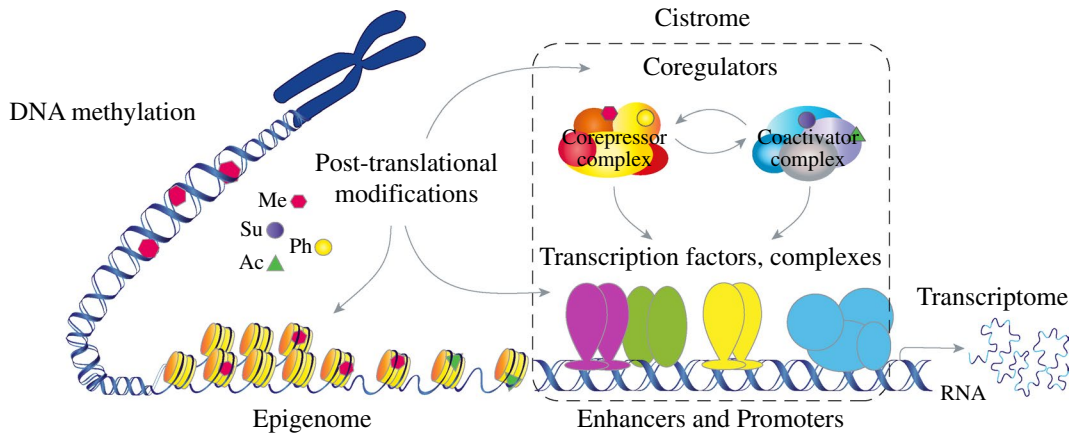

FIGURE 5 Regulatory components of gene expression. Gene expression, i.e., the transcriptome, can be modulated by several regulatory chromatin components such as DNA methylation and histone modifications, including methylation (Me), sumoylation (Su), phosphorylation (Ph), or acetylation (Ac). The cellular state of these chromatin modifications is referred to as the epigenome. Dynamic changes of both the transcriptome and epigenome require the recruitment of transcription factors and coregulators to cis-regulatory genomic DNA elements such as enhancers and promoters. The genome-wide binding profiles of these factors are referred to as the cistrome

transcription start site, and enhancers, defined as distal TF-binding regions (up to several hundred base pairs away from the transcription start site) that communicate with promoters within topologically associating domains to initiate transcription (82). Additionally, the activity of TFs depends on the recruitment of coactivator or corepressor complexes, which often contain epigenetic chromatin-modifying enzymes as subunits (83). The genome-wide chromatin binding of TFs and coregulators is termed the cistrome (Figure 5). DNA methylation is a modification that directly targets the DNA by adding a methyl group to the carbon-5 position of cytosine in CpG islands, usually associated with gene silencing. DNA methylation can potentially be the result of the interaction between genetics and the environment, which can influence metabolic homeostasis and predispose one to metabolic disease (84). It has been theorized that the nutritional status of the fetus *in utero* induces epigenetic reprogramming, preserved through generations, that can affect the metabolic outcomes in adulthood. The children of mothers who were exposed to the Dutch famine during their pregnancy showed altered DNA methylation of the imprinted insulinlike growth factor 2 gene (85) and they were predisposed to develop obesity and metabolic disease later in life. The level of DNA demethylation of mesenchymal stem cells plays an important role during lineage commitment. The treatment of the murine mesenchymal cell line C3H10T1/2 with 5-azacytidine, a methyltransferase inhibitor, results in the demethylation of the *BMP4* gene, which contributes to the commitment of mesenchymal stem cells to the adipocyte lineage (86). Several studies have also illustrated the association between obesity-related traits and DNA methylation in adipose tissue. For example, DNA methylation is different in omental and subcutaneous adipose tissue in response to gastric bypass, and it correlates with clinical traits such as fasting glucose levels (87). Several lines of evidence indicate that the human methylome can be influenced by different diets. It was shown that overfeeding with saturated fatty acids or polyunsaturated fatty acids induces different DNA methylation patterns in human adipose tissue that can predict weight increases in response to overnutrition (88).

During adipogenesis, the chromatin landscape undergoes dynamic modulations. The analysis of the whole-genome DNase I hypersensitive sites, which reveals open chromatin regions, shows that, during the early stage of adipogenesis, C/EBPβ binds with other TFs such as signal transducer and activator of transcription 5A and GR. This binding occurs at particular "hot spots" to induce chromatin remodeling that drives the recruitment of late-acting adipogenic factors such as PPARγ. Interestingly, it has been shown that some genes involved in regulation of the cell cycle are induced in a transitory manner within 2 days after induction of adipogenesis. These genes are enriched in C/EBPβ and GR binding sites, and this induction does not occur in mature adipocytes (89). In mature adipocytes, the expression of PPARγ can be regulated via a regulatory loop in cooperation with C/EBPα and coregulator complexes (90). A recent study also showed that the activity and binding of PPARγ on specific promoters can be modulated by genetic variation that influences the human response to thiazolidinedione treatments (91). Analysis of histone marks linked to transcriptional activation, such as histone H3 lysine K4 methylation (H3K4me) and histone H3 lysine K27 acetylation (H3K27ac), showed that the levels of these histone marks are increased in the distal regions of adipogenic genes during the induction of adipogenesis (92). The comparison of the genome-wide chromatin state between mouse and human models during adipogenesis has identified cis-regulatory elements, i.e., enhancers, which are different between the two models. This difference is set by the evolutionary turnover of TF-binding sites that is facilitated by the presence of distal regulatory elements at adipocyte-dependent loci (92). The genome-wide analysis of PPARγ-binding site profiles of different adipose tissue depots shows that around of 55% of these sites are overlapping between the epididymal WAT, inguinal WAT, and interscapular BAT (93), whereas 10% of PPARγ-binding sites are specific to BAT (94). This suggests that the BAT- and the

WAT-selective gene transcriptional programs are driven by a selective chromatin structure that governs specific PPARγ and C/EBP recruitment.

TRANSCRIPTIONAL COREGULATORS INVOLVED IN ADIPOGENIC PATHWAYS

Many transcriptional coregulator complexes have been identified to play a crucial role in determining the activity of TFs at specific gene loci. In general, when TFs are not bound to DNA or when they are bound to DNA but associated with corepressor complexes, gene expression is paused or silent. Upon activation, TFs undergo posttranslational modifications and conformational changes which induce either DNA binding or trigger the dynamic exchange of corepressors to coactivators and subsequently activate the transcription of target genes. Several coactivators have been identified to play important roles in adipocyte biology.

The two homologous proteins CREB-binding protein (gene name *CREBBP*) and histone acetyltransferase p300 modulate adipocyte differentiation and fat accumulation. CREB-binding protein and p300 have a histone acetyltransferase activity, mainly found at promoters and enhancers to acetylate histone H3 lysine K27, a key histone modification linked to gene activation. Heterozygous *CREBBP* knockout mice are characterized by lipodystrophy and are protected from weight gain under high-fat diet, without impacting the functionality of other organs (95). Embryonic fibroblasts from heterozygous *CREBBP* knockout mice had impaired adipogenesis as a result of reduced activation of C/EBPβ and PPARγ and inhibition of SREBP1c mediated lipogenesis. Also of importance, p300 was demonstrated to be required for adipocyte differentiation (96). The thyroid hormone receptor-associated protein (TRAP) complex, today referred to as the mediator of RNA polymerase II transcription (MED) complex, is a multiprotein complex that connects TFs to the basal transcriptional machinery assembled by RNA polymerase II. The subunit 1 of the mediator complex, known as MED1 or TRAP220, is considered a coactivator of PPARγ and thereby it regulates adipogenesis. Depletion of MED1 in embryonic fibroblasts induces the loss of their adipogenic potential (97). Recruitment of MED1 and p300 proteins is necessary for the establishment of promoter-enhancer loops at specific target genes and the activation of their transcription during adipocyte differentiation (98). Among the corepressor complexes, of particular interest for adipose tissue remodeling and functionality is the histone deacetylase 3 (HDAC3) corepressor complex.

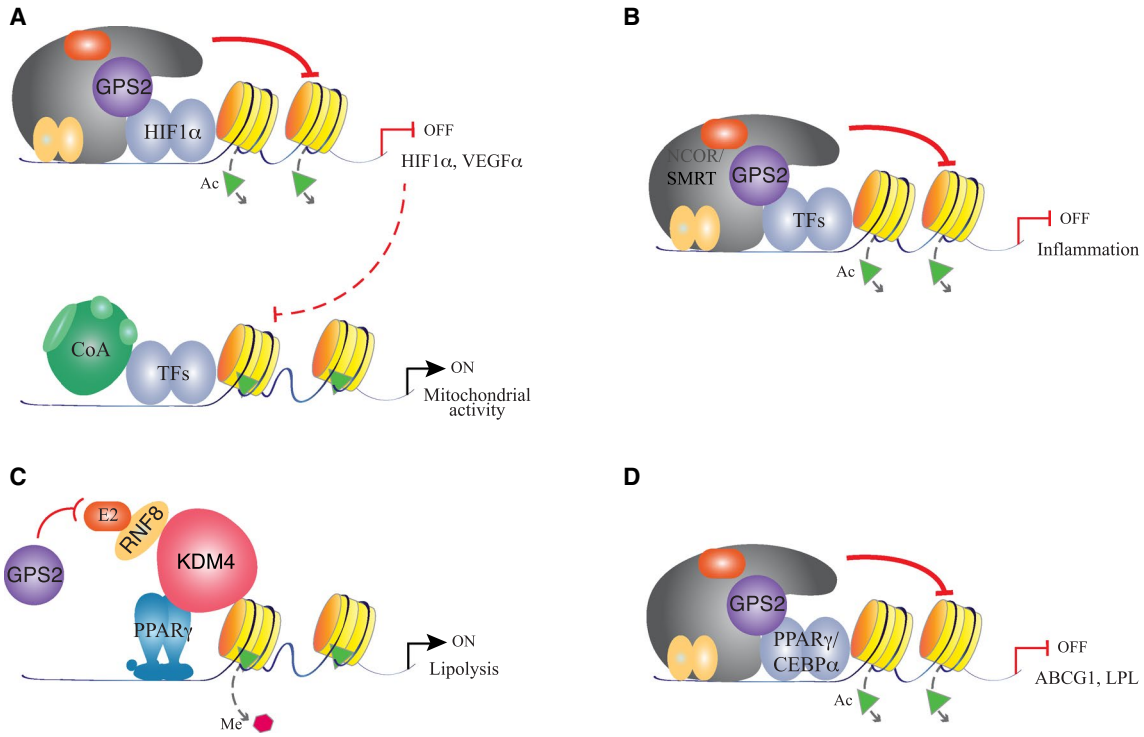

FIGURE 6 Multiple nuclear functions of GPS2 in adipocytes. (A) GPS2 inhibits the activation of HIF1α signaling and maintains proper mitochondrial function. (B) A SMRT/GPS2 corepressor complex acts on inflammatory TFs to repress proinflammatory gene expression. (C) GPS2 acts a "pioneering" coregulator by cooperating with KDM4 to create the suitable chromatin environment for the recruitment of PPARγ onto the promoters of lipolytic genes. (D) GPS2 acts as a corepressor for adipogenic TFs such as PPARγ and CEBPα to repress the expression of *ABCG1* and *LPL*, key factors for lipid accumulation in adipocytes. ABCG1, ATP-binding cassette transporter G1; CEBP, CCAAT/enhancer-binding protein; E2, ubiquti-conjugating enzyme; GPS2, G protein pathway suppressor 2; HIF1a, hypoxia-inducible factor 1a; KDM4, lysine demethylase 4A; LPL, lipoprotein lipase; Me Methylation; PPARγ, peroxisome proliferator-activated receptor γ; RNF8, ring finger protein 8; SMRT, silencing mediator of retinoid and thyroid hormone receptors; TF, transcription factor; VEGFα, vascular endothelial growth factor α

This complex contains the core subunits HDAC3, nuclear receptor corepressor 1 (NCOR1), silencing mediator for retinoid and thyroid hormone receptors (SMRT, also known as NCOR2), transducin β-like protein 1X (TBL1X), TBL-related protein 1, and G protein pathway suppressor 2 (GPS2). A variety of transgenic mouse models have increased the understanding of the function of these core subunits in adipose tissue. Adipocyte-specific *NCOR1* knockout mice display overactivation of PPARγ with increased adiposity but optimal insulin sensitivity (99). In contrast, mutant *NCOR2* mice, lacking the nuclear receptor-binding domain 1 of SMRT (encoded by the gene *NCOR2*), show hypertrophic adipocytes and insulin resistance upon diet-induced obesity (100,101). Interestingly, the hypertrophic phenotype of these mice was driven by mitochondrial dysfunction due to decreased mitochondrial biogenesis and fatty acid oxidation. A genome-wide DNA-binding profiling study using mouse 3T3-L1 cells showed that SMRT has a role as gatekeeper of adipogenesis (102), consistent with earlier data indicating that the corepressor activity of NCOR1 and SMRT on PPARγ was crucial for the inhibition of adipogenesis (103). Two independent adipocyte-specific *HDAC3* knockout models revealed opposite effects on the browning of WAT. Emmett and colleagues demonstrated that the adipocyte-specific loss of HDAC3 induces deficient WAT remodeling and browning. This suggested that HDAC3 can modulate the activity of the coactivator PGC-1α, important for *UCP1* gene transcription (104). In contrast, Ferrari and colleagues showed that specific loss of HDAC3 in adipocytes leads to browning of WAT and increases the expression of *UCP1* (105). Mice lacking TBL-related protein 1 in adipocytes showed increased adiposity and insulin resistance, likely due to impaired fasting-induced lipolysis (106).

Finally, several studies, including our own, have especially pinpointed the involvement of the subunit GPS2 in adipocyte biology. Adipocyte-specific *GPS2* knockout mice show adipose tissue expansion that predisposes to the pro-diabetic status. We propose a mechanism by which GPS2 acts as a corepressor of HIF1a and the de-repression of HIF1a induces mitochondrial dysfunction (Figure 6A) (107). In another study, we demonstrated that the expression of GPS2 is downregulated in the adipocytes of humans with obesity, thereby contributing to chromatin remodeling and transcriptional activation of key inflammatory genes including *IL6*, *IL8*, and *CCL2*, favoring adipose tissue inflammation (Figure 6B) (108). The role of GPS2 in controlling the inflammatory response in adipocytes was recapitulated *in vivo* using aP2-GPS2 transgenic mice (109). In addition, GPS2 may also have a cytoplasmic role preventing the hyperstimulation of the TNFα-induced gene program (109) or regulating the insulin-signaling pathway via protein kinase B (Akt) ubiquitination (110). Importantly, our main findings on GPS2 action in adipocytes were conserved between mice and humans (108,111). Another study unraveled an unusual mechanism of action of GPS2 as a "pioneer" factor promoting chromatin access to TFs. In this case, GPS2 was demonstrated to inhibit the E3 ubiquitin-protein ligase RNF8, thereby stabilizing the lysine-specific demethylase 4A and creating the right chromatin environment for the binding of PPARγ to the promoters of selective target genes such as *ATGL* (also known as patatin-like phospholipase domain-containing protein 2 *[PNPLA2]*) and *HSL* in 3T3-L1 adipocytes (Figure 6C) (112). More recently, we proposed a model in which loss of GPS2 in human adipocyte stem cells triggers, in the early stage of differentiation, the commitment of fibroblast-like progenitors toward the adipogenic lineage and, in the late stage of adipogenesis, adipocyte hypertrophy with a deep remodeling of their lipidome (113). The hypertrophic phenotype, linked to increased triglyceride accumulation, was triggered by increased expression of *ABCG1* and *LPL*, likely via de-repression of their promoters and enhancers. Interestingly, we found that these altered regulatory regions were co-occupied by GPS2, C/EBPα, and PPARγ (Figure 6D). Furthermore, the hypertrophic phenotype was also driven by increased LPL activity, likely via sphingomyelin depletion. Of clinical relevance, GPS2 expression was lower in individuals with obesity with type 2 diabetes compared with individuals with obesity without type 2 diabetes. Strikingly, the expression of GPS2 was inversely correlated with the expression of ABCG1, supporting the potential link of the GPS2-ABCG1 pathway to adipocyte hypertrophy in humans.

FUTURE PERSPECTIVES

As outlined throughout this paper, the substantial progress made over the past few years allows us today to better appreciate the importance of adipose tissue in the regulation of systemic metabolism. The current therapeutic approaches to reduce body weight are often unsuccessful for long-lasting results. This is because, on the one hand, they demand persistent efforts and considerable willpower from affected individuals and, on the other hand, because adipocytes have an obesogenic epigenetic memory that needs to be erased. Therefore, the remodeling of the adipocyte epigenome is emerging as a suitable therapeutic target for metabolic disease. Future studies are still necessary to dissect the relationship between the environment and the possible inheritance of altered adipocyte functionality and plasticity. Closely linked epigenome and transcriptome alterations that originate in different adipocyte subtypes/subpopulations (45), likely along with related alterations in adjacent immune cells including macrophages (111), may affect other aspects to be scrutinized, such as interorgan cross talk to pancreatic islets (22) and liver.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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