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Review

Thermogenesis in white adipose tissue: An unfinished story about PPARγ

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ABSTRACT

Background: Recruiting thermogenic adipocytes in white adipose tissue represents a potential therapeutic strategy for obesity. Interestingly, PPARγ, a major regulator of lipogenesis, is also a key factor in inducing thermogenic genes in adipose tissue.
Scope of the review: We summarize some of the recent findings regarding the biology of beige adipocytes and their potential significance for metabolic health. We also discuss the role of PPARγ in development of beige adipocyte phenotype and in inducing two apparently divergent processes, namely, lipogenesis and thermogenesis.
Major conclusions: PPARγ post-translation modifications and differential coregulator recruitment may be key factors in defining adipocyte commitment with lipogenesis or thermogenesis.
General significance: Dissecting the mechanisms underlying its thermogenic effects may prompt the development of a new generation of PPARγ-based therapies.

1. Introduction

Excessive body fat is far more than a cosmetic concern; it is a major public health problem worldwide. Obesity stems from the complex interplay between genetic, behavioral, and environmental factors that affect the balance between energy intake and energy expenditure. Currently available pharmacological approaches to treat obesity are mostly directed to reduce energy intake and show limited effectiveness on the long-term, highlighting the need for novel therapeutic strategies to induce weight loss.

Adipose tissue comprises the adipocyte, non-fat cells such as macrophages, preadipocytes, and fibroblasts, in addition to connective tissue matrix, vascular, and neural tissues [1]. This tissue is well established as a key regulator of energy homeostasis, and the last decades have witnessed an intense effort to understand its biology and dissect its role in the pathophysiology of obesity and its associated metabolic diseases.

2. White, brown, and beige: the distinct types of adipose tissue

Adipose tissue has been classically divided into two types, with origins in different precursor cells: (i) white adipose tissue (WAT), a highly complex tissue well known by its ability to store energy in the form of triglycerides, and (ii) brown adipose tissue (BAT), which shares with WAT the capacity to synthetize and store lipids but is specialized in oxidizing lipids to dissipate chemical energy in the form of heat, in a process so-called uncoupled respiration or adaptive thermogenesis. BAT was considered vestigial in human adults until recently, when the presence of genuine BAT depots in the supraclavicular and spinal regions was clearly demonstrated by functional imaging techniques and by the expression of uncoupling protein 1 (UCP-1), the marker of thermogenesis in adipocytes [2]. Interestingly, the amount of these depots was correlated to measures of metabolic health, such as lower body mass index and lower blood glucose levels [3,4].

A third type of adipocyte, named "beige" or "brite" (the latter for brown and white), was described more recently in rodents as an inducible cell type in WAT depots, upon thermogenic stimuli such as cold exposure or beta-adrenergic signalling [5]. Beige cells come from a distinct pool of progenitors in WAT depots [5], and it has been recently shown that at least a subpopulation of them originate from the smooth muscle lineage [6]. They express markers of genuine BAT, such as *Ucp1*, but have been shown to have a specific transcriptional signature, which includes *Tbx1* (encoding a developmental transcription factor), *Slc27a1* (encoding a fatty acid transporter), CD137, and CD40, both surface proteins involved in inflammatory response pathways [5]. Beige adipocytes display full thermogenic capacity and, as expected, protect mice against diet-induced obesity [7]. These cells have been also implicated in a pathological condition, namely, cancer cachexia, in which their recruitment is mediated by the action of tumor-derived parathyroid-hormone-related protein [8]. In humans, the interescapular fat depots of infants have been shown to be similar to rodent BAT, but adults exhibit depots with both brown and beige features in the cervical and interscapular region [5,9–11]. The possibility of recruiting cells with thermogenic capacity in WAT has rendered beige adipocytes as a major focus of research. There has been a great effort to identify factors that induce

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the appearance of beige cells or "browning" of WAT and, more importantly, to understand its physiological significance to total energy expenditure and nutrient homeostasis both in rodents and humans.

A myriad of factors has been shown to induce the appearance of beige adipocytes within WAT, and many of them do so by modulating either the expression or the activity of PRDM16 (PRD1-BF1-KIZ1-homologous domain containing 16). PRDM16 is a transcriptional factor that was firstly recognized by its ability to control the development of genuine brown fat from myoblastic-like *Myf5*-positive precursors [12]. More recently, it was also shown to be essential for the expression of the thermogenic genetic program in beige cells and their ability to execute uncoupled respiration [7]. Factors notable to induce browning of WAT include circulating peptides such as fibroblast growth factor 21 [13], parathyroid-related protein [8], irisin [14], and meteorin-like hormone [15]. In addition, epigenetic regulators and microRNAs (miR) targeting PRDM16 and other important transcription factors and coregulators in beige adipocyte differentiation may affect browning of WAT. Ohno et al. [16] showed that euchromatic histone-lysin *N*-methyltransferase (EHMT1) was required for both brown and beige adipocyte development. EHMT1 directly interacts with PRDM16 and induces its transcriptional activity in addition to increasing its stability by reducing its degradation. This, in turn, increases the expression a thermogenic genetic program in both brown and beige cells. Both miR-155 [17] and miR-133 [18] negatively modulate brown/beige adipocyte development and adaptive thermogenesis by targeting PRDM16 and CAAT/enhancer binding protein beta. Pharmacological agents, such as TZDs, which act as full PPARγ agonists, have also been shown to induce browning of WAT [19].

3. PPARγ and adipocyte phenotype

PPARγ is well known as the key regulator of both brown and white adipocyte differentiation [20]. This nuclear receptor (NR) has an essential role in modulating the expression of genes involved in adipogenic and lipogenic pathways [21]. It is also well established that PPARγ activation by synthetic full agonists drives browning of WAT [19], and the molecular events underlying browning of WAT upon PPARγ activation are beginning to be elucidated. Ohno et al. [22] have recently shown that PPARγ full agonists promote white-to-brown fat conversion by stabilizing PRMD16 in the liganded PPARγ complex.

Many aspects regarding the interaction between PPARγ and PRDM16 remain to be elucidated, ranging from the dependency on agonist binding to PPARγ to structural details at the atomic level. Seale et al. [12] elegantly demonstrated in fat cells that PPARγ was the only DNA-binding transcriptional factor in the PRDM16 protein complex. Using the TZD rosiglitazone as the model for PPARγ activation, they also showed using an *in vitro* assay (GST pull down) that PPARγ might interact directly with PRDM16 in a non-ligand-dependent way through two zinc-finger regions in PRDM16. Qiang et al. [23] later showed in cell-based assays (HEK293 cell line) that the interaction between PPARγ and PRDM16 was promoted by TZD. Additionally, their data indicated that TZD-induced formation of PPARγ:PRDM16 complex requires PPARγ deacetylation on two lysine residues (K268 and K293) by SirT1. This post-translational change results in clearance of the corepressor NCoR from the PPARγ complex and recruitment of PRDM16. This protein exchange, in turn, was shown to be critical for browning of WAT [23]. These lysine residues are evolutionarily conserved and lie on the helix2–helix2′ region of PPARγ ligand binding domain, next to serine at position 273 (S273). This latter amino acid, S273, is a target for cyclin-dependent kinase 5 (Cdk5), which is activated in WAT in the setting of obesity. It is worth noting that phosphorylation of PPARγ at S273 dysregulates the expression of a set of genes leading to insulin resistance. S273 phosphorylation, in turn, is directly inhibited by binding of both full [24] and partial [25] PPARγ agonists, thereby improving insulin sensitivity. Interestingly, PPARγ acetylation at K293 [23] mimics the unfavourable metabolic phenotype of phosphorylation at Ser273 [24]. Conversely, the TZD-mediated inhibition of PPARγ phosphorylation (at S273) or acetylation (at K293) similarly induces adiponectin expression, whereas only the inhibition of K293 acetylation is required for inducing thermogenic genes in WAT [23]. Collectively, these data suggest a model in which PPARγ structural modifications lead to differential coregulator recruitment to PPARγ complex to induce or inhibit the expression of thermogenic genes in WAT. Detailed understanding of the factors leading to such structural modifications, however, is still lacking.

4. Insights into PPARγ role in thermogenesis

It has been suggested that browning of WAT requires full agonism of PPARγ, as that displayed by classical TZDs, since partial agonists, such as MRL24, nTZDpa, Mbx-102, and BVT.13, have little or no effect on the expression of genes related to thermogenesis [22]. This may be viewed as an apparent paradox in the action of TZDs since full agonists induce weight gain by a number of mechanisms, including increased lipid storage in WAT. On the other hand, partial PPARγ agonists retain the insulin-sensitizing properties of TZDs without inducing weight gain.

The basis for the similar insulin-sensitizing effects of full and partial PPARγ agonists was recently shown to be, at least in part, the result of their equivalent ability to inhibit Cdk5-mediated phosphorylation of PPARγ at Ser273 [24], despite their differences in inducing the general transcriptional activity of this NHR. The differential effect of full and partial PPARγ agonists on adiposity is viewed as the result of different patterns of induction of adipogenic genes. In the light of current knowledge on the role of PPARγ in inducing a thermogenic genetic program in WAT, it would be plausible to hypothesize that the favorable effects of partial agonists on adiposity would be the result of increased induction of thermogenesis-related genes by partial over full PPARγ agonists, although this has not been observed [22]. New studies using different partial agonists (natural and synthetic compounds) may be helpful to clarify this discrepancy.

The induction of white-to-brown adipocyte conversion by full PPARγ activation raises interesting questions that to our knowledge have not been addressed in recent studies, after the availability of more detailed information on phenotypic and functional features of beige adipocytes. Since adaptive thermogenesis (lipid oxidation to generate heat, occurring in brown and brown-like/beige adipocytes) and lipogenesis (storage of chemical energy as triglycerides, the well-established action of PPARγ) intuitively seem divergent, which mechanisms would explain why activating the same NHR might drive both processes? PPARγ drives the differentiation of both white and beige adipocytes, and the factors determining the preponderance of one cell type or the other in WAT in response to PPARγ activation by full agonists remain uncertain.

It is important to state that lipogenesis and thermogenesis are not truly divergent processes. Indeed, lipogenesis is viewed as a requisite for lipolysis since it has a critical role for the maintenance of intracellular stores of triglycerides which, in turn, are required for lipolysis. Lpolysis-derived fatty acids function as substrates for thermogenesis, in addition to allosterically activating UCP-1 [26]. Accordingly, cold-exposed mice exhibit a simultaneous increase in the expression of genes related to lipogenesis (such as those encoding ATP-citrate lyase, fatty acid synthase, and glycerol-3-phosphate acyl-transferase) and lipolysis (such as that encoding monoglyceride lipase) in BAT, in association with nonshivering thermogenesis [27]. Similarly to cold exposure, PPARγ activation by full agonists has been shown to result in increased expression of genes encoding proteins related to lipogenesis [28], lipolysis [29], and thermogenesis [19,22], raising the question why this pattern of gene expression does not translate into increased energy expenditure.

Data from Lodhi et al. [30] yielded further interesting questions into the role of PPARγ in thermogenesis and the emergence of beige adipocytes. The authors showed that mice with WAT-specific knockout of the gene encoding the lipogenic enzyme fatty acid synthase (FAS) exhibited

increased energy expenditure, browning of WAT, and resistance to diet-induced weight gain, in addition to reduced expression of PPARγ target genes related to lipogenesis. Moreover, FAS knockdown in embryonic fibroblasts reduced PPARγ transcriptional activity and adipogenesis [30]. These data suggest that the inhibition of a lipogenic pathway induces browning of WAT despite concomitantly reducing PPARγ activity. Although there is plenty of data indicating that a wide range of pathways induce browning of WAT, it is intriguing that one of them is associated with reduced PPARγ activity since PRDM16 interaction with PPARγ to induce its transcriptional function seem to be important for the induction of thermogenic genes in BAT [22] and also WAT [7].

Full PPARγ activation seems to simultaneously induce the expression of genes involved in both lipogenic and thermogenic pathways in WAT but without resulting in full acquisition of thermogenic function by beige adipocytes [22]. Accordingly, Festuccia et al. [31] showed that rosiglitazone treatment reduced sympathetic activity to both BAT and WAT and also reduced thyroid status in rats. Therefore, it is plausible that other effects of PPARγ activation would favour energy storage *in vivo*, so that a subsequent factor would be necessary to activate the thermogenic machinery previously "prepared" by PPARγ. This is consistent with the observations that classical TZDs, albeit inducing the expression of thermogenesis-related genes in WAT, do not induce weight loss or increased energy expenditure [31–34], as would be expected in the setting of increased beige adipose tissue-mediated thermogenesis [35]. It is hence possible that a second regulator of WAT browning, or even other PPARγ coregulatory proteins, would be necessary for the emergence of fully competent thermogenic beige adipocytes. This has been previously shown to be the case in TZD-treated brown adipocytes, which display increased mitochondriogenesis and expression of uncoupling protein 1 (UCP1) but show full thermogenic capacity only after stimulation with norepinephrine [36]. More recently, Wu et al. [5] isolated beige cells from murine fat depots and showed that, similarly to brown adipocytes, they were responsive to adrenergic signaling, raising the possibility that other signals should act in concert with PPARγ activation to induce thermogenesis.

Another possibility to explain why PPARγ activation may drive both a lipogenic or thermogenic transcriptional program is that different environmental cues, such temperature variations or diet composition, induce different metabolic pathways involved in generating endogenous PPARγ ligands. The activation of PPARγ by distinct endogenous ligands

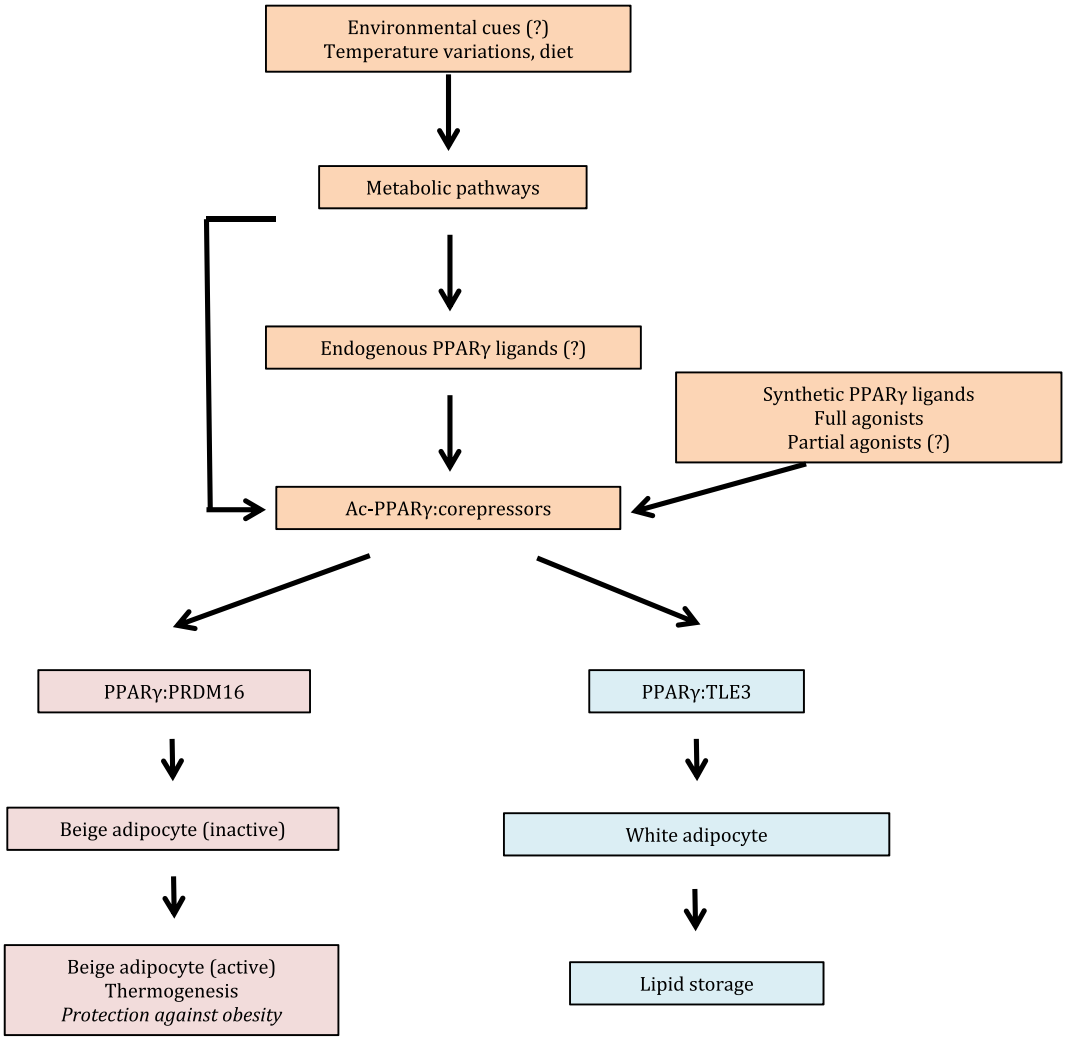

Fig. 1. Browning of white adipose tissue induced by PPARγ activation. The activation of PPARγ by full agonists, such as TZDs, may promote either lipid storage or browning in white adipose tissue, depending on differential interaction with coregulators. TZD binding may induce Sirt-1 dependent deacetylation of PPARγ at K293, which recruits PRDM16 to PPARγ complex and drives the expression of thermogenesis-related genes. Alternatively, TZD binding may induce the expression of TLE3, which interacts with PPARγ to drive the expression of lipid storage-related genes. Mechanisms driving selective recruitment of PRDM16 or TLE3 to PPARγ are not established but may involve cell-specific availability of these cofactors. It is also possible that different environmental cues, by means of the activation of differential metabolic pathways, may induce the generation of distinct endogenous PPARγ ligands that in turn promote selective recruitment of cofactors. Among synthetic PPARγ ligands, only full agonists have been shown to induce browning of white adipose tissue. Question marks indicate that the proposed events have not been established yet.

would in turn result in its interaction with different transcription coregulators, and it is plausible that PPARγ requires differential recruitment of coregulatory proteins to favor the expression of lipogenic over thermogenesis-related genes. Indeed, Villanueva et al. [37] showed that the adipogenic coregulator TLE3 interacts with PPARγ to induce a lipid storage transcriptional program and simultaneously blocks the interaction between PPARγ and PRDM16, suggesting that the interaction of PPARγ with specific coregulators, such as PRDM16 or TLE3, drives the distinct lipogenic and thermogenic effects. This raises the possibility that novel PPARγ ligands with the ability to preferentially promote recruitment of PRDM16 over TLE3 would shift PPARγ to drive preferentially the thermogenic transcriptional program and hence increase energy expenditure.

A current major interest in Biology is to understand the structure and function of transcriptional regulatory complexes. Little is known about the structural details of PPARγ:PRDM16 and PPARγ:TLE3 complexes, and these data would certainly provide new insights into how these coregulatory proteins compete for PPARγ binding to induce specific transcriptional programs. Cell-based assays indicate the presence of PRDM16 and TLE3 in PPARγ complexes. However, biochemical support for a direct interaction between PPARγ and these coregulatory proteins is lacking, raising the question whether PPARγ interacts directly with PRDM16 and TLE3, or whether binding is mediated by other proteins or small molecules. Additionally, the roles of retinoid X receptor (the obligate heterodimeric partner for PPARγ), and of the response element (at the regulatory sequence of target genes) to formation of PPARγ:PRDM16 complex, remain largely unknown.

5. Concluding remarks

In conclusion, PPARγ post-translation modifications seem to be a key factor in defining adipocyte commitment with energy storage or thermogenesis. Specifically, PPARγ acetylation status induced by differential ligand binding seems to determine distinct coregulatory recruitment (Fig. 1). Dissecting the structural and biochemical aspects of PPARγ signalling associated with differentiation and function of beige adipose tissue will certainly impact the development of next generation PPARγ-based therapies, which may include not only PPARγ modulators, but also drugs targeting specific aspects of PPARγ-regulated pathways.

Conflict of interest

We declare no conflict of interest.

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