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Review

# Brown vs white adipocytes: The PPARγ coregulator story

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ABSTRACT

**The development of adipose tissue is a process which involves the concerted cooperation of numerous transcription factors together with their coactivators and corepressors. The peroxisome proliferator-activated receptor γ (PPARγ) is considered to be one of the master regulators of adipocyte differentiation. The presence of two functionally distinct types of adipose tissue, white and brown (WAT and BAT), requires an even more complex regulation of adipose tissue development. In this review we will focus on the role of PPARγ coregulators in adipogenesis and especially on the role of PPARγ coregulators in white and brown adipose tissue. Specificity in coregulator function in WAT and BAT may form an additional level of regulation of adipose tissue development.**


## 1. White and brown adipose tissue

White adipose tissue (WAT) has long been recognized as a storage facility for excess energy derived from food intake [1]. Energy is stored in the form of triglycerides in large lipid droplets in white adipocytes. In time of caloric need lipases will hydrolyze triglycerides into fatty acids, which in turn can be oxidized in mitochondria in other tissues to generate energy [2]. More recent developments in adipose tissue research have shown that WAT is an endocrine organ, releasing a wide range of adipokines, which for example regulate immune responses, blood pressure control, angiogenesis, haemostasis, bone mass and thyroid and reproductive function [3].

Brown adipose tissue (BAT) is specialized for non-shivering thermogenesis, the process whereby the energy derived from fatty acid oxidation is used for the generation of heat due to mitochondrial uncoupling [4]. In brown adipocytes triglycerides are organized as multiple small lipid droplets, and there is a high content of mitochondria [4]. For a long time it was assumed that in humans BAT was mainly present in infants and relatively scarce in adults [5]. In contrast, small mammals, even adults, have brown adipose tissue to defend them against the cold, although the ratio WAT/BAT varies with genetic background, sex, age, nutritional status and environmental conditions [6]. Three recent studies, using the glucose tracer 2-[18F]-fluoro-D-deoxy-D-glucose (FDG) in combination with computer tomography, showed that also human adults have distinct BAT deposits [7–9]. In addition, cold induced FDG uptake, an important characteristic of BAT activity, was fourfold higher in lean compared to overweight/obese individuals [8].

White and brown adipocytes both are derived from mesenchymal stem cells (MSC; see Fig. 1a). Precursor cells of WAT reside in the mural cell compartments of the adipose vasculature and are positive for PPARγ and CD24 expression (reviewed in [10]). Lineage-tracing experiments in mice have shown that brown adipocytes are derived from *Myf5* positive progenitor cells, which also give rise to myocytes, while white adipocytes are *Myf5* negative [11]. Brown adipocytes have been detected in WAT after chronic cold exposure or β-adrenergic stimulation [12] and these cells did not originate from the *Myf5* positive progenitor cells [11]. Such brown adipocytes, which clearly have a distinct developmental origin from brown adipocytes in BAT, are sometimes referred to as "brite" or "beige" adipocytes.

Several cell culture models are used to study adipogenesis. The most widely used model system for preadipocyte differentiation is the 3T3-L1 cell line. This cell line, derived from Swiss 3T3 mouse embryos [13], can be differentiated into mature white adipocytes upon treatment with an adipogenic cocktail containing insulin, dexamethasone and IBMX. Knock-down or ectopic overexpression experiments in 3T3-L1 cells is very often used to study the adipogenic potential of proteins, as can also be seen in this review. Other cell systems used to study adipogenesis include primary

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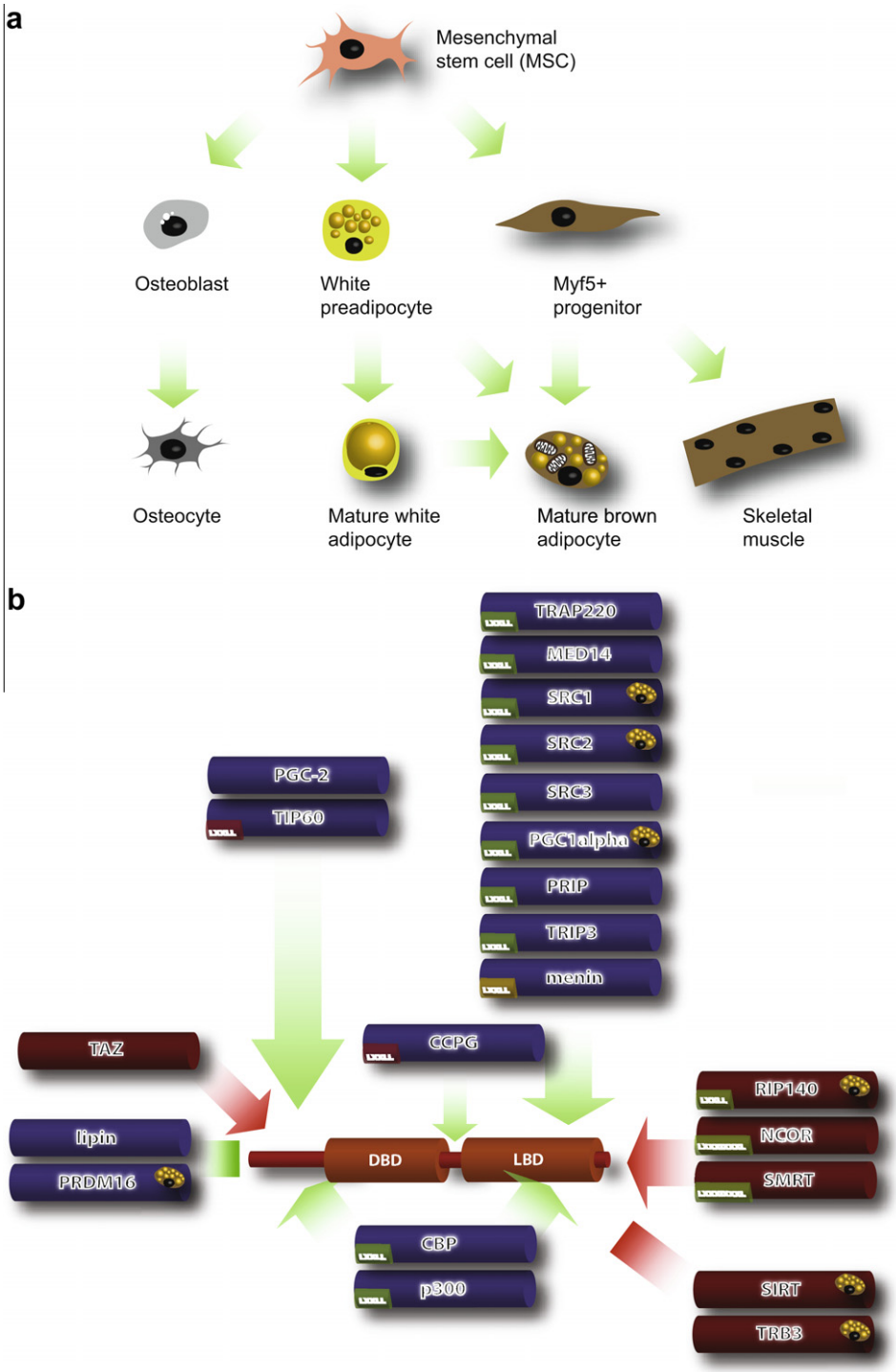



**Fig. 1.** White and brown adipocyte differentiation and adipogenesis-specific PPARγ coregulators. (a) Schematic representation of the differentiation of mesenchymal stem cells (MSCs) towards white and brown adipocytes. Cell fate of brown and white adipocytes is determined by their precursors; white adipocytes are derived from *Myf5* negative preadipocytes, while brown adipocytes are originated from *Myf5* positive precursors, which also can give rise to skeletal muscle cells. PPARγ coregulators. White preadipocytes can be forced to differentiate into brown-like (also referred to as "brite" or "beige") adipocytes, with many of the properties of brown adipocytes, although these cells have an independent developmental origin. (b) Overview of coactivators (in blue) and corepressors (in red) of PPARγ (orange) involved in adipogenesis. The DNA bindin domain (DBD) and ligand-binding domain (LBD) of PPARγ are marked. The presence of one or more NR boxes in coactivators is depicted by LXXLL. When a NR box is involved in the interaction of PPARγ with the coactivator, the box is green, otherwise the box is red. In case of menin the status of the NR box in the interaction with PPARγ is unclear and therefore contains a brown label. The presence of one or more CoRNR boxes is represented by LXXXIXXXL and the involvement of a box in the interaction with PPARγ is depicted by green (involved) or red (not involved). The arrowheads indicate the domain of PPARγ to which the coregulators bind. In the absence of an arrowhead, there is an interaction, but the PPARγ domain involved has not been determined yet. Finally, the brown fat cell icons represent coregulators involved in determining white/brown adipocyte identity.

fibroblasts, embryonic stem cells, immortalized fibroblast cell lines (for example 3T3-NIH), multipotent precursor cells isolated from adult tissues and other preadipocyte cell lines (including 3T3-F442A, hMADs and SGBS) [14–16].

## 2. The role of PPARγ in white and brown adipogenesis

Although white and brown adipocytes follow different routes from mesenchymal stem cell to adipocyte, they share a similar transcriptional program. In both cell types PPARγ is a key regulator of differentiation, as has been shown in several genetic knockout studies [17–19], as well as in numerous cell-based studies (see this review). PPARγ is a member of the peroxisome proliferator-activated receptor family, of which the firstly identified PPARα was able to respond to various compounds that induce peroxisome proliferation [20]. PPARγ was identified based on homology and on studies regarding the transcriptional control of the *FABP*4 gene [21–23]. Like other members of the PPAR family, PPARγ is a ligand dependent transcription factor which regulates target genes upon binding to to PPARγ Responsive Elements (PPREs) after dimerization with RXRs [24,25]. Synthetic PPARγ agonists include the thiazolidinediones (TZDs), which ameliorate insulin resistance and lower blood glucose levels in patients with type 2 diabetes [26]. The domain structure of PPARγ is that of most nuclear receptors (NRs). The N-terminus contains a transcriptional activation domain (AF-1) whose function is ligand-independent. This domain is subject to various post-translational modifications (reviewed in [27]). The C-terminus harbours a ligand dependent transcriptional activation domain (AF-2), forms the ligand-binding domain (LBD) and is involved in ligand dependent coregulator interactions (Fig. 1). Due to alternative promoter usage and alternative splicing two PPARγ isoforms exist: PPARγ1 and PPARγ2, the latter having a 28 (human) or 30 (mouse) amino acids longer N-terminus [28]. Both isoforms are strongly induced during preadipocyte differentiation [29], but the functional difference still remains elusive.

PPARγ directly controls the expression of many genes involved in they key functions of adipocytes, like lipid transport, lipid metabolism, insulin signalling and adipokine production [30]. PPARγ target genes involved in lipid metabolism regulate processes like lipid transport (*FABP4*) [22], fatty acid uptake (*LPL*, *FATP/SLC27A1*, *OLR1*) [31–33], recycling of intracellular fatty acids (*PEPCK/PCK1*, *GK*, *AQP7*) [34–36] and lipolysis (*GPR81*) [37]. An important mechanism by which PPARγ regulates insulin sensitivity is through the expression of adipokines. For example, adiponectin expression is increased in adipocytes upon PPARγ ligand stimulation, while resistin and TNFα are decreased [38].

The relative new methods of chromatin IP followed by deep sequencing (ChIP-seq) or microarray analysis (ChIP-chip) have identified more than 5000 regions where PPARγ can bind in the genome of differentiated 3T3-L1 cells [39–41]. Amongst these regions a considerable amount of genes was identified involved in glucose and lipid metabolic processes and these regions also showed enhanced RNA polymerase II occupancy and transcription in adipogenesis [40].

## 3. The role of PPARγ coregulators in white and brown adipogenesis

Since PPARγ is important in both WAT and BAT development, the specific gene regulatory programs for WAT and BAT may be explained by tissue-specific transcription factors than PPARγ, or by differences in activity, usage or expression of certain PPARγ coregulators. In general, NRs activate transcription of target genes in concert and in association with coregulatory proteins, a class of proteins that do not bind to DNA themselves. The route from target gene binding by a NR to gene transcription is a multistep process which in general involves both recruitment and release of coregulators, chromatin remodelling and activation of the basal transcription machinery. Coregulators may effect chromatin remodelling, as is the case with for instance the p300 and CBP coregulators. Both proteins contain histone acetyl transferase (HAT) activity and are able to acetylate nucleosomal histones in target genes, leading to altered chromatin state an altered accessibility for the polymerase II transcription machinery [42]. Other coregulators act as a direct or indirect bridge between NRs and the basal transcription machinery, hereby enhancing or inhibiting NR-mediated gene transcription [43,44]. The Mediator complex proteins form a well described example of such bridging proteins [45]. Interactions between coregulators and NRs can be regulated by ligands, as exemplified by the "classical" coactivator SRC-1. Upon ligand stimulation the NR changes conformation which enables the interaction between the LXXLL motif in SRC-1 and the "charge clamp" in the LBD of NRs [46,47]. SMRT and NCOR were the first corepressors identified [48,49], and both contain the CoRNR box motif (LXXXIXXXL/I) [50] which, similar to the LXXLL motif, forms an amphipathic helix and binds to the charge clamp of NRs. Upon ligand stimulation the affinity for the CoRNR box motif is reduced, leading to release of the corepressor molecules.

### 3.1. Steroid Receptor Coactivator (SRC) family of coactivators

The first NR coactivator discovered was the Steroid Receptor Coactivator-1 (SRC-1) [47], originally identified as a coactivator for the steroid receptor superfamily. SRC-1 also interacts with PPARγ via LXXLL motifs in a ligand dependent manner [51,52]. Also for the closely related SRC-2/TIF2 and SRC-3 proteins a direct, ligand-dependent, interaction has been shown [53,54], and we have shown that PPARγ can bind SRC-2 and SRC-3 LXXLL motifs in a ligand dependent fashion [55]. The metabolic role of SRC family members emanated from studies with SRC-1 and SRC-2 deficient mice. SRC-$1^{-/-}$ mice are prone to obesity since they display reduced energy expenditure, on the other hand SRC-$2^{-/-}$ mice show increased adaptive thermogenesis due to hyperactive BAT, resulting in reduced weight gain, improved glucose tolerance and insulin sensitivity [53]. The effects of SRC-1 and SRC-2 on metabolism are predominantly mediated by PGC1α (see below). This coregulator, which controls mitochondrial biogenesis and β-oxidation, is upregulated in SRC-2-depleted BAT. In addition, in SRC-$2^{-/-}$ mice the interaction between SRC-1 and PGC1α is facilitated, leading to an increase in the thermogenic activity of PGC1α [53]. More recently it was shown that also SRC-3 plays in important role in adipogenesis. SRC-$3^{-/-}$ mice exhibit reduced weight compared to wild type control mice, and it was suggested that this effect is caused by a defect in terminal adipocyte differentiation and fat accumulation in WAT [56]. The SRC-$1^{-/-}$/SRC-$3^{-/-}$ double knockout mice are lean, resistant to high-fat-diet induced obesity, with no BAT lipid storage, decreased UCP1 expression and defective adaptive thermogenesis. Despite the higher food intake in these animals, these animals show increased basal metabolic rates and enhanced physical activity, resulting in a lean phenotype [57].

In conclusion, these observations suggest that SRC-1 and SRC-2 control the energy balance between WAT and BAT, whereby SRC-1 promotes energy expenditure via fatty acid oxidation in BAT. SRC-2 represses this process by activation of PPARγ in WAT, leading to an increase in triglyceride accumulation in WAT and a decrease in free fatty acids.

### 3.2. p300 and CBP

p300 and CREB-binding protein (CBP) are histone acetyl transferases [58,59] and are well known as NR coactivators. These two proteins share a high degree of homology, although distinct functions have been described [42]. Both proteins interact with the LBD of PPARγ in a ligand- and LxxLL-dependent fashion, while at the same time an interaction can be established with the AF-1 domain of PPARγ [60]. p300 and CBP are capable of enhancing the

transcriptional activity of both AF-1 and AF-2 domain separately. Although studies have shown that both proteins are indispensable for 3T3-L1 differentiation, the role of p300 and CBP in adipose biology has not been firmly established yet [61]. Furthermore CBP$^{+/-}$ mice display reduced weight of WAT due to reduced triglyceride accumulation in WAT, but no BAT phenotype. Also these mice are more insulin sensitive, more glucose tolerant and protected from high-fat diet induced weight gain [62]. The differential effect on WAT and BAT development observed in CBP$^{+/-}$ mice suggests that CBP is mainly functional in WAT. The effect of p300 depletion on adipose depots in mice is not known: p300$^{-/-}$ mice are fully embryonic lethal, while p300$^{+/-}$ are partial embryonic lethal [63].

Bugge et al. have recently compared target gene regulation of PPARγ lacking the A/B domain with that of WT PPARγ [64]. The expression of only a small number of genes depended on the A/B-domain. Interestingly, recruitment of p300 and CBP to these genes was reduced, suggesting that the A/B domain of PPARγ is specifically involved in the recruitment or stabilization of CBP- and p300-containing cofactor complexes to a subset of target genes. In conclusion, there are several indications showing the involvement of CBP and p300 in adipogenesis, but additional studies are required to establish how PPARγ, p300 and CBP cooperate to regulate adipogenesis in both WAT and BAT.

### 3.3. PPARγ Coactivator-1 (PGC-1) family of coactivators

PGC-1α was originally identified in a two-hybrid experiment using murine BAT cDNA and PPARγ as bait [65]. The related *PGC-1β* gene was subsequently identified by homology database searches [66]. PGC-1α contains three LXXLL motifs and binds to several NRs, in general in a ligand dependent manner (reviewed by [67]). The interaction with PPARγ however is ligand-independent and mediated through a N-terminal domain and an LXXLL motif [65,68]. It should be noted that PGC-1 coactivators also target other transcription factors involved in metabolism, like FOXO1, SREBP, Foxa2 and Sox9 [69–72].

The physiological role of PGC-1 has been demonstrated in PGC-1 knockout mouse strains. PGC-1α$^{-/-}$ mice have a reduced expression of mitochondrial genes in, amongst others, BAT, skeletal and cardiac muscles and the brain, resulting in an impaired metabolic response to stresses like cold exposure and starvation [73,74]. This is in line with the role of PGC-1α as a cold induced coactivater regulating the expression of mitochondrial genes involved in adaptive thermogenesis, like UCP1 [65]. In PGC-1β$^{-/-}$ mice, mitochondrial gene expression is also decreased in several tissues, including BAT, liver, brain, skeletal and cardiac muscle [75,76], and these mice are impaired in their adaptive thermogenesis after cold exposure. This suggests that at least in mice PGC-1β plays a non-redundant role in the control of mitochondrial oxidative energy metabolism.

The role of gene regulation by PPARγ in concert with PGC-1 has not been studied extensively. PGC-1α, a PPARγ target gene itself [77], enhances PPARγ-mediated UCP1 expression [65]. On the other hand there are also indications that the expression of UCP1 can be regulated by other means, since also in BAT devoid of PPARγ UCP1 is expressed [78]. The classical PPARγ target gene FABP4 is not regulated by PGC-1α [65], while regulation of the glycerol kinase (GyK) gene by PPARγ does involve PGC-1α., showing that there is gene target selectivity for PGC-1α [79]. To conclude, PGC1-α and PGC1-β are important for mitochondrial oxidative metabolism and hence for BAT function. They are highly differentially expressed in BAT and WAT which reflects their BAT-specific function. There are indications that PPARγ is involved in PGC1-α and PGC1-β mediated BAT-specific functions, but more extensive studies are required to further elucidate the role of PPARγ in BAT function.

### 3.4. Mediator subunits: TRAP220 and MED14

TRAP220 and MED14 are subunits of the Mediator complex. This complex does not contain enzymatic activity, but is involved in bridging the RNA polymerase II machinery with other coactivators [45]. TRAP220 was identified as a NR interacting protein in a two-hybrid screen using PPARγ as bait [80]. TRAP220 interacts with PPARγ in a ligand- and LXXLL-dependent way [80,81] and its presence is required for PPARγ2-stimulated adipogenesis of mouse embryonic fibroblasts (MEFs) [82]. Recently it was shown that in undifferentiated TRAP220$^{-/-}$ MEFs, exogenous PPARγ could be recruited to and activate the *FABP4* gene [83]. These findings suggest that, depending on the cellular condition, TRAP220 is not per se required for PPARγ transcriptional activity, but there might be redundancy with other Mediator subunits. In the same study it was shown that both LXXLL motifs are dispensable for rescue of adipogenesis in TRAP220$^{-/-}$ MEFs, while on the other hand intact LXXLL motifs were essential for PPARγ function in a cell-free transcription assay. This suggests that in a cellular context, TRAP220 is required for PPARγ mediated adipogenesis, but a direct interaction with PPARγ is not required.

The TRAP220 knockout mouse is not viable and dies around embryonic day 11.5 due to defects in the development of placental vasculature and due to cardiac failure [84,85]. To our knowledge it is unknown if in heterozygous TRAP220$^{+/-}$ mice adipogenesis is affected. In general the role of TRAP220 in WAT and BAT development has been studied scarcely. It has been reported that TRAP220 is expressed in mouse BAT [86] and that it is involved in PGC-1α mediated UCP1 expression [87]. Future studies with for instance conditional knockout mice might shed light on the specific role of TRAP220 in WAT and BAT.

Recently the Mediator subunit MED14 has been identified as a novel PPARγ coactivator involved in 3T3-L1 adipogenesis [88]. MED14 does not contain LXXLL motifs and interacts with the N-terminus of PPARγ in a ligand-independent manner. In addition, MED14 mediates the binding of PPARγ, MED6 and MED8 to the proximal promoter of the *FABP4* gene, but it is not involved in PPARγ binding to the *FABP4* enhancer. Specific roles for MED14 in either BAT or WAT have not been described yet.

### 3.5. Other PPARγ coregulators

In addition to the coregulators described above, also a number of less well studied coregulators with a role in adipogenesis have been identified recently.

Lipin-1 was originally identified as the mutant gene underlying lipodystrophy in the fatty liver dystrophy (*fld*) mouse [89]. The *fld* mouse lacks both normal WAT and BAT, reflecting an overall requirement for Lipin-1 in adipocyte differentiation. Lipin-1 deficient cells and tissue fail to induce the expression of PPARγ and C/EBPα and hence their downstream target genes [90]. Next to its ability to induce PPARγ expression, Lipin-1 probably also acts as a PPARγ coactivator, as was demonstrated by the recruitment of Lipin-1 to the PPRE of the PPARγ target gene PEPCK [91]. mRNA levels of Lipin-1 are equal in murine BAT and WAT [92], indeed suggesting a general role for Lipin-1 in adipocyte differentiation.

Tip60, a member of the MYST family of acetyltransferases, was identified by mass spectrometry as a novel PPARγ coregulator [93]. It coactivates PPARγ via and interacts with the PPARγ AF-1 region and its acetyltransferase capacity is required for this activation. In addition, knock down of Tip60 abrogates 3T3-L1 adipocyte differentiation.

Multiple Endocrine Neoplasia type 1 (MEN1) patients frequently contain mutations in the *MEN1* gene, encoding the menin protein [94]. MEN1 patients often develop lipomas, while PPARγ is expressed in several MEN1-associated tumors. Menin is a subunit

of a MLL1/MLL2 containing protein complex which methylates lysine 4 of histone H3. Recently menin was identified as a coactivator for PPARγ [95]. Menin contains an LXXLL motif, but interacts with the AF-2 of PPARγ in a ligand- and LXXLL-independent way. Remarkably, PPARγ mediated gene activation by menin is ligand dependent and requires both an intact LXXLL motif as well as an intact PPARγ helix 12. Both knock down studies in 3T3-L1 cells and experiments in MEN1$^{-/-}$ fibroblasts show that menin is required for adipocyte differentiation [95].

CCPG (Constitutive Coactivator of PPARγ) is another PPARγ coactivator identified by two-hybrid screening. CCPG interacts with the hinge/D region of PPARγ in a ligand-independent manner and enhances the transactivation of PPARγ [96]. Although the CCPG protein contains four LXXLL motifs, none of them is required for the interaction with PPARγ. Overexpression or knock down experiments in OP9 preadipocytes has shown that CCPG is involved in the proces of adipogenesis [96].

The Thyroid Interacting Protein 3, Trip3, was originally identified as an interaction partner of the Thyroid Hormone Receptor [97]. Using a microarray based method to study the interaction between peptides containing LXXLL motifs derived from NR coactivators and the LBD of PPARγ, we found that the LXXLL motif of TRIP3 interacts with PPARγ in a ligand dependent manner [55]. Knockdown of TRIP3 in 3T3-L1 cells led to impaired adipocyte differentiation, showing its potential importance in adipogenesis.

PRIP (PPAR Interacting Protein) was identified in a two-hybrid screen using PPARγ as bait. PRIP interacts ligand-dependently and via a LXXLL motif with PPARγ and activates PPARγ transcription in a ligand dependent way [98]. PRIP knockout mice are embryonic lethal, however PRIP$^{-/-}$ MEFs exhibit impaired PPARγ-mediated adipogenesis, suggesting that coactivation of PPARγ by PRIP is required for adipogenesis.

Castillo et al. [99] performed a two-hybrid screen with the AF-1 domain of PPARγ. One of the interacting proteins they identified was PGC-2/SCAND1. PGC-2 is able to increase the transcriptional activity of PPARγ and overexpression of PGC-2 in 3T3-L1 cells leads to increased adipocyte differentiation. No mouse model is available for PGC-2 and no specific role for PGC-2 has been described in WAT or BAT.

### 3.6. PRDM16

By comparing the mRNA expression levels of transcription-related genes in mouse WAT and BAT, Seal and co-workers identified PRDM16 as a BAT-specific transcription factor [100]. PRDM16 is a zinc finger protein which was first identified at a chromosomal breakpoint in myeloid leukemia [101]. Overexpression of PRDM16 in cultured white preadipocytes results in activation of the brown adipose differentiation program, with upregulation of mitochondrial genes. This is accompanied by an increase of mitochondrial biogenesis and uncoupled respiration, hallmarks of BAT. In contrast, knock down of PRDM16 in brown adipocytes ablates the brown adipocyte characteristics [100]. These data highly suggests that PRDM16 serves as a molecular switch which determines adipose tissue to become white or brown. In a follow-up study, the role of PRDM16 was further specified as being a cell fate switch between skeletal myoblasts and brown adipocytes [11], two cell types which both are derived from *myf5* positive precursor cells. Indeed, PRDM16 is able to induce brown adipogenesis in myogenic cells [11]. PRDM16 deficient mice die at birth, but late-stage embryos (E17) show severely affected BAT, with decreased expression of BAT selective and thermogenic genes, and simultaneously enhanced expression of skeletal myogenic genes [11]. PRDM16 immunopurification followed by mass spectrometry analysis identified PPARγ as a component of the PRDM16 complex. PRDM16 is able to bind to PPARγ in a ligand-independent manner and enhances the transcriptional activity of PPARγ. PRDM16 is unable to promote adipogenesis in PPARγ$^{-/-}$ fibroblasts and the conversion of primary myoblasts by PRDM16 is largely dependent on the presence of the TZD rosiglitazone. This indicates that PPARγ activation is required for the adipogenic function of PRDM16. Hence, PRDM16 not only works as a DNA binding transcription factor, but also as a PPARγ coactivator.

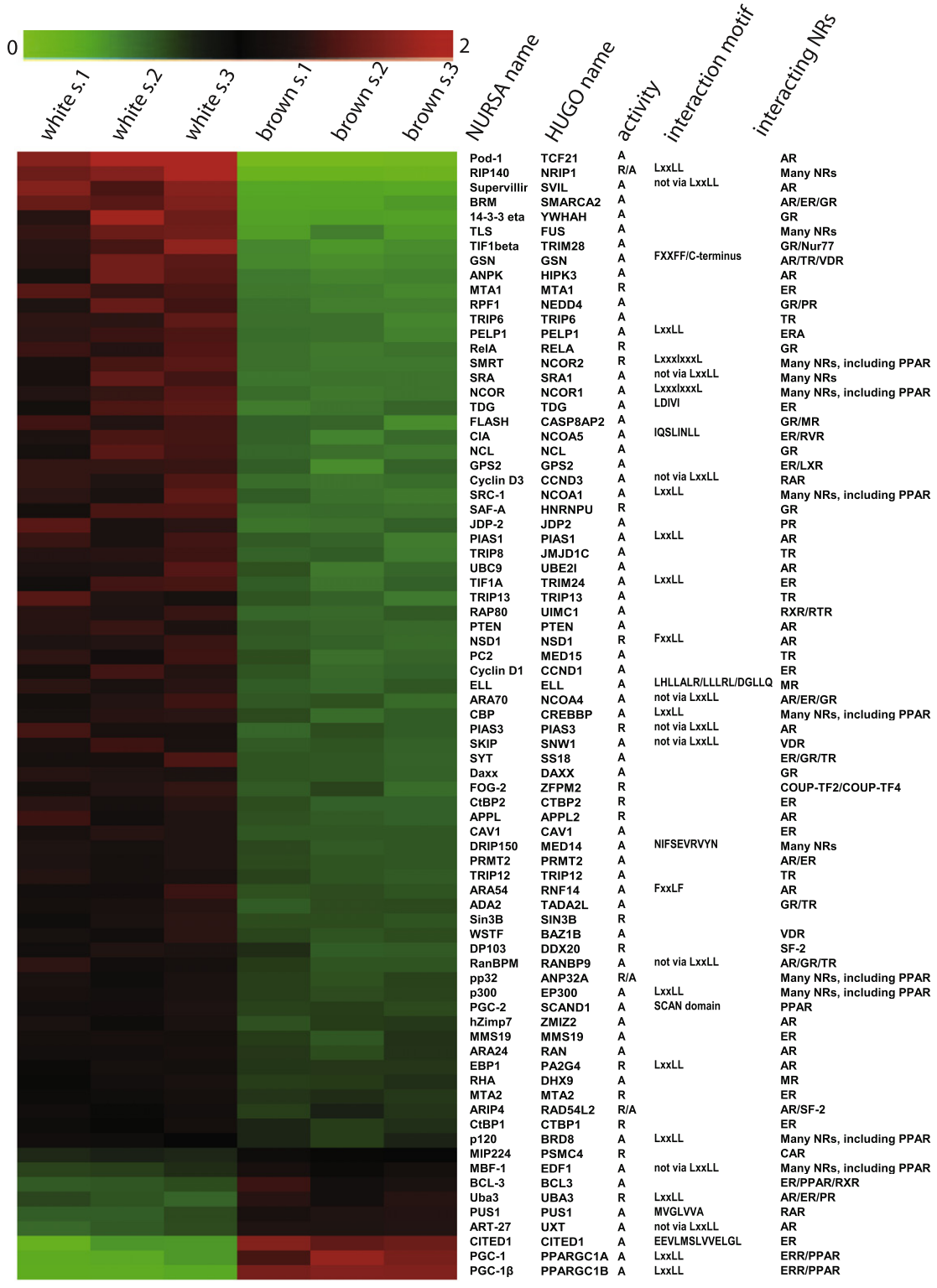
### 3.7. NCoR, SMRT and other corepressor proteins

NCoR and SMRT were the first identified NR corepressors [48,49]. Both proteins form complexes which contain histone deacetylation activity (reviewed in [102]). NCoR and SMRT are highly homologous, and contain three and two CoRNR boxes, respectively [50,103–106]. Both NCoR$^{-/-}$ and SMRT$^{-/-}$ mice display an embryonic lethal phenotype. The NCoR$^{-/-}$ mice display defects in CNS, erythrocyte and thymocyte development, while the SMRT$^{-/-}$ mice have aberrant forebrain structures and die due to a lethal heart defect [107,108]. Nofsinger et al. generated a knock-in mutation in the receptor interacting domain of SMRT, which disrupts its interaction with NRs. These mice exhibit a number of metabolic defects, including improved insulin sensitivity and increased adiposity, which were attributed to enhanced PPARγ activity [109]. SMRT$^{+/-}$ mice develop increased adiposity on a high-fat diet and MEFs derived from these mice show increased adipogenesis. Also insulin sensitivity was enhanced in SMRT$^{+/-}$ adipocytes [110]. In the 3T3-L1 system PPARγ2 is able to recruit NCoR and SMRT and both coregulators repress PPARγ2-mediated gene transcription [106]. Additional studies showed the recruitment of NCoR and SMRT to PPARγ target genes in a promoter specific way. PPARγ recruits NCoR and SMRT to the glycerol kinase promoter and both corepressors are released upon ligand stimulation. However, in case of the aP2 promoter there is no recruitment of either corepressors [79].

The differential role of NCoR and SMRT in WAT and BAT physiology is not clear. To our knowledge, no studies have been performed to analyse the specific role of NCoR and SMRT in both WAT and BAT.

SIRT1, a NAD$^+$-dependent deacetylase, interacts with PPARγ and represses PPARγ mediated transcription by docking with NCOR and SMRT [111]. SIRT1 binds to the aP2 promoter upon fasting and SIRT$^{+/-}$ mice displayed a decreased release of free fatty acids upon fasting. Furthermore, overexpression of SIRT1 triggers lipogenesis and adipogenesis [111]. These data imply that SIRT1 is involved in the regulation of adipogenesis by PPARγ upon caloric restriction. It was hypothesized that SIRT1 might be involved in regulating the brown adipocyte differentiation by preventing myoblast differentiation as well as promoting mitochondrial biogenesis [112]. Comparison of gene expression profiles of SIRT1 overexpressing myoblasts and differentiating brown pre-adipocytes showed a large overlap of regulated genes, which strengthens this hypothesis.

The Receptor Interacting Protein 140 (RIP140) is a NR coregulator which is involved in both activation and repression of NR-mediated transcription (reviewed in [113]). It contains nine LXXLL motifs and four repression domains and mainly acts as a scaffold that links NRs to chromatin remodelling enzymes. RIP140 is able to interact with PPARγ in a ligand dependent way [114] and we have shown that some of the LXXLL motifs of RIP140 interact with PPARγ in a ligand dependent manner [55]. Physiologically, RIP140 is involved in regulating the energy expenditure in adipose tissue. RIP140$^{-/-}$ mice are leaner than their control littermates, which is not due to a defect in adipogenesis, but which is caused by derepression of energy expenditure genes (e.g. UCP1) in WAT [115,116]. This latter observation suggests that RIP140 suppresses brown adipose specific gene transcription in WAT.




| NURSA name | HUGO name | activity | interaction motif | interacting NRs |
|---|---|---|---|---|
| Pod-1 | TCF21 | A | | AR |
| RIP140 | NRIP1 | R/A | LxxLL | Many NRs |
| Supervillir | SVIL | A | not via LxxLL | AR |
| BRM | SMARCA2 | A | | AR/ER/GR |
| 14-3-3 eta | YWHAH | A | | GR |
| TLS | FUS | A | | Many NRs |
| TIF1beta | TRIM28 | A | | GR/Nur77 |
| GSN | GSN | A | FXXFF/C-terminus | AR/TR/VDR |
| ANPK | HIPK3 | A | | AR |
| MTA1 | MTA1 | R | | ER |
| RPF1 | NEDD4 | A | | GR/PR |
| TRIP6 | TRIP6 | A | | TR |
| PELP1 | PELP1 | A | LxxLL | ERA |
| RelA | RELA | R | | GR |
| SMRT | NCOR2 | R | LxxxIxxxL | Many NRs, including PPAR |
| SRA | SRA1 | A | not via LxxLL | Many NRs |
| NCOR | NCOR1 | A | LxxxIxxxL | Many NRs, including PPAR |
| TDG | TDG | A | LDIVI | ER |
| FLASH | CASP8AP2 | A | | GR/MR |
| CIA | NCOA5 | A | IQSLINLL | ER/RVR |
| NCL | NCL | A | | GR |
| GPS2 | GPS2 | A | | ER/LXR |
| Cyclin D3 | CCND3 | A | not via LxxLL | RAR |
| SRC-1 | NCOA1 | A | LxxLL | Many NRs, including PPAR |
| SAF-A | HNRNPU | R | | GR |
| JDP-2 | JDP2 | A | | PR |
| PIAS1 | PIAS1 | A | LxxLL | AR |
| TRIP8 | JMJD1C | A | | TR |
| UBC9 | UBE2I | A | | AR |
| TIF1A | TRIM24 | A | LxxLL | ER |
| TRIP13 | TRIP13 | A | | TR |
| RAP80 | UIMC1 | A | | RXR/RTR |
| PTEN | PTEN | A | | AR |
| NSD1 | NSD1 | R | FxxLL | AR |
| PC2 | MED15 | A | | TR |
| Cyclin D1 | CCND1 | A | | ER |
| ELL | ELL | A | LHLLALR/LLLRL/DGLLQ | MR |
| ARA70 | NCOA4 | A | not via LxxLL | AR/ER/GR |
| CBP | CREBBP | A | LxxLL | Many NRs, including PPAR |
| PIAS3 | PIAS3 | R | not via LxxLL | AR |
| SKIP | SNW1 | A | not via LxxLL | VDR |
| SYT | SS18 | A | | ER/GR/TR |
| Daxx | DAXX | A | | GR |
| FOG-2 | ZFPM2 | R | | COUP-TF2/COUP-TF4 |
| CtBP2 | CTBP2 | R | | ER |
| APPL | APPL2 | R | | AR |
| CAV1 | CAV1 | A | | ER |
| DRIP150 | MED14 | A | NIFSEVRVYN | Many NRs |
| PRMT2 | PRMT2 | A | | AR/ER |
| TRIP12 | TRIP12 | A | | TR |
| ARA54 | RNF14 | A | FxxLF | AR |
| ADA2 | TADA2L | A | | GR/TR |
| Sin3B | SIN3B | R | | |
| WSTF | BAZ1B | A | | VDR |
| DP103 | DDX20 | R | | SF-2 |
| RanBPM | RANBP9 | A | not via LxxLL | AR/GR/TR |
| pp32 | ANP32A | R/A | | Many NRs, including PPAR |
| p300 | EP300 | A | LxxLL | Many NRs, including PPAR |
| PGC-2 | SCAND1 | A | SCAN domain | PPAR |
| hZimp7 | ZMIZ2 | A | | AR |
| MMS19 | MMS19 | A | | ER |
| ARA24 | RAN | A | | AR |
| EBP1 | PA2G4 | R | LxxLL | AR |
| RHA | DHX9 | A | | MR |
| MTA2 | MTA2 | R | | ER |
| ARIP4 | RAD54L2 | R/A | | AR/SF-2 |
| CtBP1 | CTBP1 | R | | ER |
| p120 | BRD8 | A | LxxLL | Many NRs, including PPAR |
| MIP224 | PSMC4 | R | | CAR |
| MBF-1 | EDF1 | A | not via LxxLL | Many NRs, including PPAR |
| BCL-3 | BCL3 | A | | ER/PPAR/RXR |
| Uba3 | UBA3 | R | LxxLL | AR/ER/PR |
| PUS1 | PUS1 | A | MVGLVVA | RAR |
| ART-27 | UXT | A | not via LxxLL | AR |
| CITED1 | CITED1 | A | EEVLMSLVVELGL | ER |
| PGC-1 | PPARGC1A | A | LxxLL | ERR/PPAR |
| PGC-1β | PPARGC1B | A | LxxLL | ERR/PPAR |

**Fig. 2.** Differential expression of NR coregulators in mouse WAT and BAT. Microarray data from Seale et a. [100] was retrieved from the Gene Expression Omnibus site of the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE8044). This set contains gene expression profiles of three samples of mouse epididymal WAT (white s.1–s.3) and three samples of interscapular BAT (brown s.1-s.3), all analysed with the Affymetrix Mouse Genome 430 2.0 Array platform. We coupled the list of all NR coregulators known in the Nuclear Receptor Signalling Atlas (NURSA) database to the gene expression dataset and compared expression of NR coregulators in WAT and BAT using the Student's *t*-test. We depicted all the NR coregulators which are differentially expressed ($P < 0.001$). For each gene the expression is normalized to the average expression of that particular gene in the six samples. The names of the coregulators according to the NURSA website and the Human Genome Organization (HUGO) are depicted, as well as the activity (A = activating, R = repressing, A/R = both activating and repressing), the motifs involved in the interaction and the interacting NRs.

Recently, the role of the TRB3 corepressor in adipogenesis has been reported. TRB3 encodes a kinase involved in promoting lipid metabolism during fasting. Qi et al. generated transgene mice containing TRB3 under the control of the aP2 promoter [117]. These mice display a lean phenotype, with reduced weight of WAT, whereas BAT mass is not decreased. Although this effect was attributed to the inactivation of acetyl-coenzyme A carboxylase, it also has been reported that TRB3 interacts with PPARγ, whereby it inhibits PPARγ mediated transcription, leading to suppression of adipocyte differentiaton [118]. The observation that TRB3 overexpression had no effects on BAT, suggests that its action is specific for WAT.

The final corepressor which will be discussed here is TAZ. The function of this protein is largely unknown, but it can act as a transcriptional coactivator or corepressor [119]. Hong and co-workers demonstrated that TAZ is able to modulate the differentiation of MSCs into osteoblasts or adipocytes: TAZ represses adipogenesis by inhibiting PPARγ-dependent transcription, while at the same time stimulating osteoblast differentiation by stimulating the transcription factor Runx2. Furthermore, knockdown of TAZ in 3T3-L1 cells resulted in increased adipocyte differentiation [120], underscoring the repressive function of TAZ in adipogenesis. A direct interaction between TAZ and the AF-1 domain of PPARγ has been shown which requires the TAZ WW domain. The study of Hong et al. [120] shows that TAZ can determine the cellular fate of MSCs; whether TAZ is also involved in BAT development is currently unknown.

## 4. Identification of new PPARγ coregulators involved in WAT and BAT development

In this paper a number of PPARγ coregulators involved in adipogenesis have passed in review. Also a selected set of these coregulators is involved in the development of WAT or BAT specifically. Since over 250 NR coregulators (www.nursa.org) have been identified to date, it may be expected that there are more PPARγ coregulators involved in white and/or brown adipogenesis. We used the microarray datasets of Seale et al. [100] in combination with the list of NR coregulators from the Nuclear Receptor Signalling Atlas (www.nursa.org), to identify NR coregulators differentially expressed in WAT versus BAT (Fig. 2). This microarray dataset contains gene expression profiles of three murine WAT samples and three BAT samples of three male C57Bl/6 mice at 10–12 weeks of age. In Fig. 2 we listed 77 coregulators which show differential expression. Strikingly, 68 coregulators displayed higher expression in WAT compared to BAT, while only 9 genes displayed a higher expression in BAT than in WAT. Interestingly, the mRNA expression levels of the corepressors NCoR and SMRT are higher in WAT than in BAT. It may therefore be hypothesized that both proteins might be involved in determining the distinctive properties of WAT and BAT, for instance by repressing brown-specific PPARγ target genes in WAT, as already has been shown for the repression of *UCP1* by RIP140 in WAT [115,116]. To investigate this possibility it is necessary to study the physiological role of NCoR and SMRT in WAT and BAT in more detail. In addition, it would be interesting to over-express NCoR and SMRT in brown adipocytes to see if a transition from brown to white phenotype can be effectuated. CBP mRNA expression is higher in WAT than in BAT, suggesting a WAT-specific role for CBP. This is in line with the $CBP^{+/-}$ mouse model, where WAT is affected and not BAT [62]. Strikingly, also the p300 mRNA expression is higher in WAT than in BAT, also suggesting that p300 might be involved in WAT and BAT specificity. The higher expression of SRC-1 in WAT is surprising, since SRC-1 together with PGC1α is involved in regulating adaptive thermogenesis [53]. The microarray data also shows that PGC-2 expression is higher in WAT compared to BAT, suggesting that also this coactivator may be involved in WAT-specific PPARγ transcription. Both PGC-1α and PGC-1β displayed a higher expression in BAT than in WAT, which is in accordance with the role of the PGC-1 proteins in BAT mediated adaptive thermogenesis.

A number of coregulators discussed in this review, including Tip60, menin, CCPG and TRIP3, do not show differential expression, indicating that these coregulators may have general, and not BAT- or WAT-specific functions in adipocyte differentiation. More research with (conditional) mouse models in combination with experiments in white and brown adipocyte cells is required to further address the specific function of these coregulators in BAT and WAT.

The list presented in Fig. 2 also includes a large number of coregulators which have not been associated with PPARγ thus far. It would be interesting to further investigate these coregulators for (i) a possible interaction with PPARγ, (ii) their role in adipogenesis, and (iii) their specific roles in WAT and BAT.

## 5. Conclusions and perspectives

The interest in the mechanisms underlying WAT and BAT development has increased the last few years, not in the least because conversion of WAT into BAT may be therapeutically beneficial in the fight against obesity and its associated disorders. The discovery that BAT is present in human adults together with the discovery of PRDM16 as a BAT determinant has raised the interest in this subject considerably. Although PRDM16 is an important player in the development of BAT, it is likely that there are more proteins involved in determining adipocyte fate. In this review we have focused on PPARγ coregulators which are involved in adipogenesis in general and WAT and BAT development in particular. So far, only few PPARγ coregulators have been reported to have specific roles in WAT and BAT specification (SRC-1, SRC-2, RIP140 and PGC-1α). On the other hand, a number of coregulators we have discussed show differential expression in WAT compared to BAT, including NCOR, SMRT and p300, suggesting that these coregulators might also be involved in determining BAT/WAT identity. In addition, more NR coregulators show differential expression, although it is unknown if these coregulators mediate PPARγ signalling. Future research could give insight in the role of these coregulators in WAT and BAT and could provide us with new targets for therapeutic intervention in the treatment of obesity.

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