Review Article

PPARs Integrate the Mammalian Clock and Energy Metabolism

Lihong Chen and Guangrui Yang

The Institute for Translational Medicine and Therapeutics, Translational Research Center, University of Pennsylvania, 3400 Civic Center Boulevard, Building 421, Philadelphia, PA 19104-5158, USA

Correspondence should be addressed to Lihong Chen; bjclh2000@163.com and Guangrui Yang; guangrui@mail.med.upenn.edu

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors that function as transcription factors regulating the expression of numerous target genes. PPARs play an essential role in various physiological and pathological processes, especially in energy metabolism. It has long been known that metabolism and circadian clocks are tightly intertwined. However, the mechanism of how they influence each other is not fully understood. Recently, all three PPAR isoforms were found to be rhythmically expressed in given mouse tissues. Among them, PPARα and PPARγ are direct regulators of core clock components, Bmal1 and Rev-erbα, and, conversely, PPARα is also a direct Bmal1 target gene. More importantly, recent studies using knockout mice revealed that all PPARs exert given functions in a circadian manner. These findings demonstrated a novel role of PPARs as regulators in correlating circadian rhythm and metabolism. In this review, we summarize advances in our understanding of PPARs in circadian regulation.

1. Introduction

1.1. The PPAR Family. Peroxisome proliferator-activated receptors (PPARs) are transcription factors, belonging to the nuclear receptor superfamily, a group of proteins that are usually activated by their respective ligands and function within the cell nuclei for controlling metabolism, development, and homeostasis of the organism. PPARs heterodimerize with the retinoid X receptor (RXR) and bind to PPAR responsive element (PPRE) in the regulatory region of target genes that function in diverse biological processes, such as lipid metabolism, adipogenesis, insulin sensitivity, immune response, and cell growth and differentiation [1, 2]. PPARs also participate in the pathogenesis of a cluster of human diseases, for example, metabolic syndrome that includes insulin resistance, glucose intolerance, obesity, dyslipidemia, hypertension, atherosclerosis, and microalbuminuria [3–6].

PPARs have 3 isoforms in mammals, namely, α, β/δ, and γ. Although they share structural similarity and exhibit high homology in amino acid sequence, the three isoforms are differentially expressed among tissues [7]. In general, PPARα is abundant in the liver, brown adipose tissue, heart, and kidney; PPARγ is mainly enriched in the adipose tissue and

PPARβ/δ is ubiquitously expressed throughout the body [8]. Their differential distributions as well as different affinities to ligands attribute to their distinct roles. PPAR ligands vary from endogenous fatty acids to industrial chemicals and pharmaceutical drugs. Synthetic PPARα agonists such as fenofibrate and clofibrate are clinically proven lipid-lowering drugs [9]. A class of PPARγ ligands called thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, has been introduced in clinical practice for improving glycemic control via insulin sensitization in patients with type 2 diabetes [10]. Increasing evidence also points to a potential role of PPARβ/δ activators in improving insulin resistance and dyslipidemia [11]. In addition, some PPAR ligands are also potential therapeutic agents for treating hypertension, atherosclerosis, and diabetic nephropathy [1, 12, 13]. The development and use of PPAR ligands in the past decades have greatly advanced our understanding of physiological and pathological role of PPARs and the therapeutic implication of targeting them.

1.2. Circadian Rhythm. Circadian rhythm is any biological process displaying endogenous and entrainable oscillations of about 24 hours. In mammals, for example, sleep-awake

pattern, blood pressure and heart rate, hormone secretion, body temperature, and energy metabolism exhibit circadian oscillation. These endogenous responses have significant relevance to human health and diseases [14]. Disruption of circadian rhythm has become an exacerbating factor in metabolic syndrome [15–19]. This is exceptionally important in developed countries due to frequent shift working, exposure to artificial light, travel by transmeridian air flight, and involvement in social activities. Some reports have shown that night-shift workers exhibit a higher incidence of obesity and other aspects of metabolic syndrome [15, 20, 21]. Recently, Hatori and colleagues found that temporal restriction of calorie consumption limits mouse weight gain on a high fat diet via enhancing oscillation of clock genes and their target genes [22]. Deletion of the clock gene Bmal1 (brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1) in adipose tissue causes mice to become obese via shifting their eating behavior [23]. These evidence suggested when you eat may be as important as what you eat.

Circadian rhythm is driven by a group of genes called clock genes and has been widely observed in plants, animals and even in bacteria. In mammals, the core clock genes are rhythmically expressed in the SCN (suprachiasmatic nucleus), the master clock residing in the hypothalamus, and most peripheral tissues such as liver, fat, muscle, heart, and blood vessels [14]. These genes form a tightly regulated system with interlocking feedback and feedforward loops (Figure 1). BMAL1 and CLOCK (Circadian Locomotor Output Cycles Kaput), or its paralog NPAS2 (neuronal PAS domain protein 2), form a heterodimer. This BMAL1:CLOCK/NPAS2 complex binds to E-box elements in the promoters of Period (PER1-3) and Cryptochrome (CRY1 and CRY2) genes and activates their transcription. Upon accumulation in the cytoplasm to a critical level, the proteins of PER and CRY dimerize and translocate into the nucleus to repress the transcriptional activity of BMAL1:CLOCK/NPAS2 complex, thereby shutting down their own transcription. This core loop is interconnected with additional regulatory loops involving nuclear receptors, RAR-related orphan receptor (ROR), and REV-ERB, whose transcription is driven by BMAL1 and in turn to enhance and suppress BMAL1 transcription, respectively [24]. These feedback loops also control numerous target genes (termed clock controlled genes, CCG) in a circadian manner. Recently, all PPAR isoforms in mouse tissues were found to be rhythmically expressed [25]. Furthermore, PPARα and PPARγ have direct interactions with the core clock genes [26–28], suggesting that they may act as molecular links between circadian rhythm and energy metabolism.
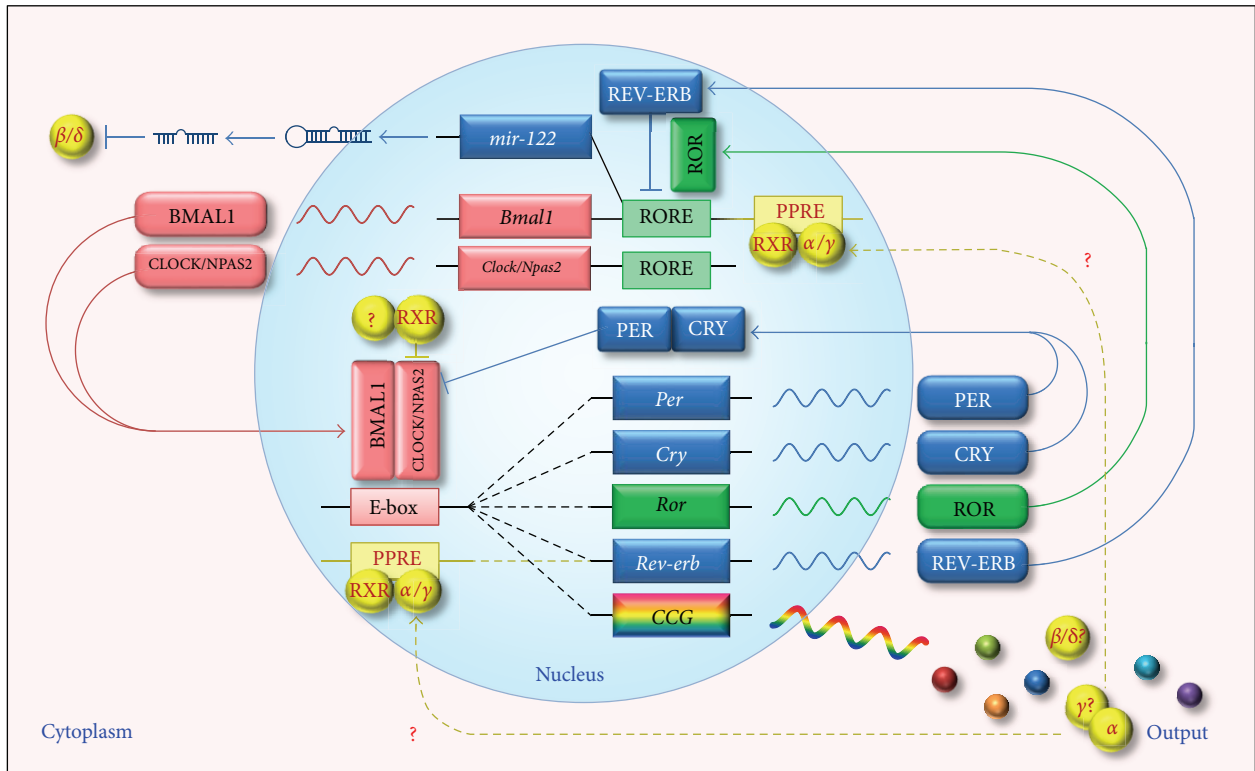
2. PPARα and Circadian Clock

The expression of PPARα has a diurnal rhythm in mouse liver, heart, kidney, and, to a lesser extent, in the SCN [25, 29]. This circadian pattern might be partially controlled by some hormonal factors, such as glucocorticoids and insulin, whose secretions display diurnal variations [29, 30]. More recently, several reports showed a direct link between PPARα and the circadian clocks. Firstly, PPARα was identified as a direct target gene of BMAL1 and CLOCK via an E-box-dependent mechanism [31]. The expression level of PPARα in the liver was decreased and its circadian oscillation was abolished in BMAL1 knockout mice or CLOCK-mutant mice [27, 31]. Reciprocally, PPARα-null mice showed altered oscillation of BMAL1 and PER3 in the liver. *In vitro* experiments revealed that PPARα directly regulates the transcription of BMAL1 and REV-ERBα via binding to PPRE sites in their respective promoter regions [27, 32]. Besides transcriptional regulation, PPARα could modulate PER2 activity by direct physical interactions [33].

Fenofibrate, a PPARα agonist and anticholesterol drug, was able to increase transcription and reset rhythmic expression of BMAL1, PER1, PER3, and REV-ERBα in mouse livers [27] and cultured hepatocytes [32]. Bezafibrate, another PPARα agonist, was shown to phase-advance the circadian expression of BMAL1, PER2, and REV-ERBα in multiple mouse peripheral tissues [34, 35]. Interestingly, bezafibrate did not alter the phase of core clock genes in the SCN, although it was able to affect circadian behavior, for example, alleviating delayed sleep phase syndrome caused by clock mutation [34]. In addition, clock gene expressions were also found unaltered in the SCN of PPARα knockout mice [27]. These results imply that PPARα is involved in circadian regulation independently of the central clock and that PPARα could be a potent target for treating sleep disorders.

More importantly, as a mediator of circadian regulation of lipid metabolism, PPARα also regulates the expression of numerous genes involved in lipid and cholesterol metabolism and energy homeostasis. Many of these genes, such as sterol regulatory element binding protein (SREBP), fatty acid synthase (FAS), and HMG-CoA reductase, display daily fluctuations in mouse liver; however, their amplitudes are attenuated or abolished in PPARα knockout mice [36, 37]. Kersten et al. showed that PPARα mRNA is induced during fasting in wild-type mice to accommodate the increased requirement of hepatic fatty acid oxidation. PPARα-null mice, however, showed a massive accumulation of lipid in their livers when fasted [38], which indicates a pivotal role of PPARα in the management of energy storage during fasting. Oleoylethanolamide (OEA), an endogenous PPARα agonist, is synthesized diurnally in the gut epithelium [39]. Administration of OEA produced satiety and reduced weight gain in wild-type mice, but this response was abolished in PPARα-null mice [40], suggesting that PPARα regulates the feeding behavior and may be a potential target for treating eating disorders.

PPARα is also abundant in the heart where it serves a role in normal cardiac metabolic homeostasis via regulating enzymes involved in fatty acid beta-oxidation [41]. Its higher expression level during early dark phase is consistent with the circadian variation of heart function. Wu et al. found that both PPARα and its target gene glucose transporter type 4 (Glut4) and acetyl-coA synthetase (Acs1) were significantly downregulated in the activity phase in mouse heart when cardiac tissue overexpressed PPARγ coactivator 1α (PGC-1α). The disrupted circadian expression of PPARα was accompanied by abolished diurnal variation of ejection fraction and shortening fraction [42], indicating that PPARα

α: PPARα.   β/δ : PPAR β/δ.
γ: PPARγ.   CCG: clock controlled gene.

FIGURE 1: Involvement of PPARs in the transcriptional feedback loops of the mammalian circadian clock. BMAL1:CLOCK/NPAS2 heterodimer activates transcription of PER, CRY, ROR, and REV-ERB via binding to E-box in their promoters. Upon accumulation, PER and CRY dimerize and translocate into the nucleus to repress BMAL1:CLOCK/NPAS2 activity and therefore their own transcription. ROR activates and REV-ERB represses RORE-mediated transcription. These interlocking loops also control numerous output genes in a circadian manner. In addition, PPARs are integrated in this system (shown in yellow). PPARα and PPARγ regulate the expression of BMAL1 and REV-ERB via binding to PPRE in their promoters. PPARα is also a direct target gene of BMAL1. PPARβ/δ is a target for miR-122 whose transcription is inhibited by REV-ERB. Besides, as the PPAR partner, RXR inhibits the transcriptional activity of BMAL1:CLOCK/NPAS2 complex via binding to CLOCK or NPAS2. All PPARs display circadian expression pattern in given tissues; however, it is still not known if γ or β/δ isoform is directly regulated by Bmal1 or if the integration of PPARs in circadian clock system forms a closed loop.

plays a critical role in connecting circadian biology to heart performance.

3. PPARγ and Circadian Clock

PPARγ is a key regulator of adipogenesis and is well known for serving as a therapeutic target for treating metabolic diseases. Agonists of PPARγ rosiglitazone and pioglitazone have been widely used for many years for treating type 2 diabetes, owing to their effectiveness in promoting insulin sensitivity. Recently, PPARγ was shown to exhibit a remarkable circadian expression pattern in mouse liver, fat, and blood vessels [25, 28]. Global deletion of PPARγ in mice abolished or dampened circadian rhythms at both behavioral and cellular levels [43].

Day-night variations in the blood pressure (BP) and heart rate (HR) are among the best known circadian rhythms of physiology. Vascular conditional deletion of PPARγ in mice

dampened diurnal variations of HR and BP via deregulation of BMAL1 [28]. Yang et al. found that global deletion of PPARγ abolished these rhythms even without affecting loco-motor activity under regular light/dark conditions [43]. In addition, pioglitazone has been shown to transform BP from a nondipper to a dipper type in type 2 diabetic patients [44]. These findings strongly support an essential role of PPARγ in maintaining circadian rhythms of BP and HR, which may partially explain the beneficial side effects of PPARγ agonists in cardiovascular system.

Moreover, several other key factors related to PPARγ play important roles in circadian rhythm. Notably, REV-ERBα, a target gene of PPARγ [45], is one of the core clock components, although there has not been a direct evidence showing that PPARγ exerts circadian function via REV-ERBα yet. PPARγ coactivator 1α (PGC-1α) is also identified as a circadian factor. PGC-1α is rhythmically expressed in mouse liver and muscle and positively regulates BMAL1, CLOCK, and REV-ERBα [46]. Mice lacking PGC-1α show abnormal

locomotor activity and disrupted diurnal oscillation of body temperature and energy metabolism, which is correlated with aberrant expression pattern of metabolic genes and clock genes [46]. Nocturnin, a clock controlled gene, binds to PPARγ and enhance its transcriptional activity [47]. Deletion of nocturnin abolished PPARγ oscillation in the liver of mice fed on high-fat diet, accompanied by a decrease in expression of many genes related to lipid metabolism [48]. 15-Deoxy-D 12,14-prostaglandin J$_2$ (15d-PGJ$_2$), a natural PPARγ ligand, was reported to be an entrainment factor *in vitro* [49], while its circadian function was abolished by PPARγ deletion [43].

4. PPARβ/δ and Circadian Clock

Despite accumulating evidence supporting the role of PPARβ/δ in metabolic control and energy homeostasis [6, 50] and abundant data showing association between metabolism and circadian rhythm [51], little is known concerning the influence of PPARβ/δ in circadian rhythm unlike PPARα and PPARγ, even though mRNA level of PPARβ/δ is cyclic in mouse liver and brown adipose tissue [25]. REV-ERBα and miR-122 may serve as a possible link between PPARβ/δ and circadian clock. miR-122 is a highly abundant, liver-specific microRNA whose transcription is regulated by REV-ERBα. It has previously been shown to regulate lipid metabolism in mouse liver [52]. Gatfield et al. proved PPARβ/δ as a new target for miR-122, suggesting that PPARβ/δ might act as a circadian metabolic regulator in miR-122-mediated metabolic control [53]. Recently, Challet et al. observed oscillations in PPARβ/δ expression in hamster SCN. Administration of PPARβ/δ agonist L-16504 amplified the delay phase of locomotor response induced by a light pulse [54], indicating that PPARβ/δ may play a role in circadian behavior. In another recent paper, Liu et al. revealed a PPARβ/δ-dependent diurnal oscillation of *de novo* lipogenesis in mouse liver [55]. Using hepatocyte specific knockout mice, they found that PPARβ/δ controls temporal expression of hepatic lipogenic genes including acetyl-CoA carboxylase 1 (ACC1), ACC2, FAS, and stearoyl-CoA desaturase-1 (SCD1), thus affecting fatty acid metabolism in the liver.

In addition, RXRα, the partner of all PPARs, interacts with CLOCK protein in a ligand-dependent manner to inhibit CLOCK:BMAL1-dependent transcriptional activation of clock gene expression in vascular cells [56]. However, it is still not known whether its circadian function is dependent on PPARs. If this is the case, PPARβ/δ may be the dominant partner since α and γ isoforms were reported to be positive regulators for BMAL1 [27, 28].

5. Conclusions and Future Directions

Within the family of nuclear receptors, ROR and REV-ERB have been identified as core clock components. Recent findings suggest their closest phylogenetic neighbor PPARs as circadian regulators as well. PPARs have been extensively demonstrated as effective molecular targets for treating metabolic diseases. Circadian oscillations of PPARs and their target genes display a strong association with energy and metabolism homeostasis. The aberration of PPARs-circadian clock system could result in altered expression of metabolic genes, leading to disturbance in energy status. Therefore, the diseases jointly regulated by PPARs and the circadian clock have become an exploratory area. Further investigation into the regulation of PPARs in circadian rhythmic diseases could strengthen our understanding of mechanisms for disorders in energy homeostasis and metabolism and may provide novel therapeutic avenues for the treatment of metabolic ailments.

Things to keep in mind, however, most of the current studies were from mouse models. The extent to which mouse models simulate responses in human is still controversial, especially for circadian research since humans are diurnal. To date, the circadian expression of PPARα in human fibroblasts [31] and PPARγ in human adipose explants [57] has been identified, while how they link energy metabolism and circadian clock in humans remains to be determined.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

References

[1] J. Wu, L. Chen, D. Zhang et al., "Peroxisome proliferator-activated receptors and renal diseases," *Frontiers in Bioscience*, vol. 14, no. 3, pp. 995–1009, 2009.

[2] Y. Guan, J. Yang, L. Chen et al., "PPARs and female reproduction: evidence from genetically manipulated mice," *PPAR Research*, vol. 2008, Article ID 723243, 2008.

[3] Y. Guan, "Peroxisome proliferator-activated receptor family and its relationship to renal complications of the metabolic syndrome," *Journal of the American Society of Nephrology*, vol. 15, no. 11, pp. 2801–2815, 2004.

[4] H. Takano and I. Komuro, "Peroxisome proliferator-activated receptor γ and cardiovascular diseases," *Circulation Journal*, vol. 73, no. 2, pp. 214–220, 2009.

[5] A. Y. Y. Cheng and L. A. Leiter, "PPAR-alpha: therapeutic role in diabetes-related cardiovascular disease," *Diabetes, Obesity and Metabolism*, vol. 10, no. 9, pp. 691–698, 2008.

[6] T. Coll, R. Rodríguez-Calvo, E. Barroso et al., "Peroxisome Proliferator-Activated Receptor (PPAR) β/δ: a new potential therapeutic target for the treatment of metabolic syndrome," *Current Molecular Pharmacology*, vol. 2, no. 1, pp. 46–55, 2009.

[7] B. Desvergne and W. Wahli, "Peroxisome proliferator-activated receptors: nuclear control of metabolism," *Endocrine Reviews*, vol. 20, no. 5, pp. 649–688, 1999.

[8] O. Braissant, F. Foufelle, C. Scotto, M. Dauça, and W. Wahli, "Differential expression of Peroxisome Proliferator-Activated Receptors (PPARs): tissue distribution of PPAR-α, -β, and -γ in the adult rat," *Endocrinology*, vol. 137, no. 1, pp. 354–366, 1996.

[9] B. Staels, J. Dallongeville, J. Auwerx, K. Schoonjans, E. Leitersdorf, and J.-C. Fruchart, "Mechanism of action of fibrates on

lipid and lipoprotein metabolism," *Circulation*, vol. 98, no. 19, pp. 2088–2093, 1998.

[10] A. B. Jones, "Peroxisome Proliferator-Activated Receptor (PPAR) modulators: diabetes and beyond," *Medicinal Research Reviews*, vol. 21, no. 6, pp. 540–552, 2001.

[11] M. D. Leibowitz, C. Fiévet, N. Hennuyer et al., "Activation of PPARδ alters lipid metabolism in db/db mice," *FEBS Letters*, vol. 473, no. 3, pp. 333–336, 2000.

[12] S. Z. Duan, M. G. Usher, and R. M. Mortensen, "PPARs: the vasculature, inflammation and hypertension," *Current Opinion in Nephrology and Hypertension*, vol. 18, no. 2, pp. 128–133, 2009.

[13] C. W. Park, Y. Zhang, X. Zhang et al., "PPARα agonist fenofibrate improves diabetic nephropathy in db/db mic," *Kidney International*, vol. 69, no. 9, pp. 1511–1517, 2006.

[14] G. Yang, G. Paschos, A. M. Curtis, E. S. Musiek, S. C. McLoughlin, and G. A. Fitzgerald, "Knitting up the raveled sleave of care," *Science Translational Medicine*, vol. 5, no. 212, Article ID 212rv3, 2013.

[15] B. Karlsson, A. Knutsson, and B. Lindahl, "Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people," *Occupational and Environmental Medicine*, vol. 58, no. 11, pp. 747–752, 2001.

[16] J. E. Gangwisch, D. Malaspina, B. Boden-Albala, and S. B. Heymsfield, "Inadequate sleep as a risk factor for obesity: analyses of the NHANES I," *Sleep*, vol. 28, no. 10, pp. 1289–1296, 2005.

[17] J.-P. Chaput, M. Brunet, and A. Tremblay, "Relationship between short sleeping hours and childhood overweight/obesity: results from the "Québec en Forme" project," *International Journal of Obesity*, vol. 30, no. 7, pp. 1080–1085, 2006.

[18] C. Gallou-Kabani, A. Vigé, and C. Junien, "Lifelong circadian and epigenetic drifts in metabolic syndrome," *Epigenetics*, vol. 2, no. 3, pp. 137–146, 2007.

[19] E. Maury, K. M. Ramsey, and J. Bass, "Circadian rhythms and metabolic syndrome: from experimental genetics to human disease," *Circulation Research*, vol. 106, no. 3, pp. 447–462, 2010.

[20] B. Karlsson, "Commentary: metabolic syndrome as a result of shift work exposure?" *International Journal of Epidemiology*, vol. 38, no. 3, pp. 854–855, 2009.

[21] U. Holmbäck, A. Forslund, A. Lowden et al., "Endocrine responses to nocturnal eating—possible implications for night work," *European Journal of Nutrition*, vol. 42, no. 2, pp. 75–83, 2003.

[22] M. Hatori, C. Vollmers, A. Zarrinpar et al., "Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet," *Cell Metabolism*, vol. 15, no. 6, pp. 848–860, 2012.

[23] G. K. Paschos, S. Ibrahim, W. L. Song et al., "Obesity in mice with adipocyte-specific deletion of clock component Arntl," *Nature Medicine*, vol. 18, no. 12, pp. 1768–1777, 2012.

[24] H. R. Ueda, W. Chen, A. Adachi et al., "A transcription factor response element for gene expression during circadian night," *Nature*, vol. 418, no. 6897, pp. 534–539, 2002.

[25] X. Yang, M. Downes, R. T. Yu et al., "Nuclear receptor expression links the circadian clock to metabolism," *Cell*, vol. 126, no. 4, pp. 801–810, 2006.

[26] I. Inoue, Y. Shinoda, M. Ikeda et al., "CLOCK/BMAL1 is involved in lipid metabolism via transactivation of the Peroxisome Proliferator-Activated Receptor (PPAR) response element," *Journal of Atherosclerosis and Thrombosis*, vol. 12, no. 3, pp. 169–174, 2005.

[27] L. Canaple, J. Rambaud, O. Dkhissi-Benyahya et al., "Reciprocal regulation of brain and muscle Arnt-like protein 1 and peroxisome proliferator-activated receptor α defines a novel positive feedback loop in the rodent liver circadian clock," *Molecular Endocrinology*, vol. 20, no. 8, pp. 1715–1727, 2006.

[28] N. Wang, G. Yang, Z. Jia et al., "Vascular PPARγ controls circadian variation in blood pressure and heart rate through Bmal1," *Cell Metabolism*, vol. 8, no. 6, pp. 482–491, 2008.

[29] T. Lemberger, R. Saladin, M. Vázquez et al., "Expression of the peroxisome proliferator-activated receptor α gene is stimulated by stress and follows a diurnal rhythm," *Journal of Biological Chemistry*, vol. 271, no. 3, pp. 1764–1769, 1996.

[30] H. H. Steineger, H. N. Sorensen, J. D. Tugwood, S. Skrede, O. Spydevold, and K. M. Gautvik, "Dexamethasone and insulin demonstrate marked and opposite regulation of the steady-state mRNA level of the Peroxismal Proliferator-Activated Receptor (PPAR) in hepatic cells. Hormonal modulation of fatty-acid-induced transcription," *European Journal of Biochemistry*, vol. 225, no. 3, pp. 967–974, 1994.

[31] K. Oishi, H. Shirai, and N. Ishida, "CLOCK is involved in the circadian transactivation of peroxisome- proliferator-activated receptor α (PPARα) in mice," *Biochemical Journal*, vol. 386, no. 3, pp. 575–581, 2005.

[32] P. Gervois, S. Chopin-Delannoy, A. Fadel et al., "Fibrates increase human REV-ERBα expression in liver via a novel peroxisome proliferator-activated receptor response element," *Molecular Endocrinology*, vol. 13, no. 3, pp. 400–409, 1999.

[33] I. Schmutz, J. A. Ripperger, S. Baeriswyl-Aebischer, and U. Albrecht, "The mammalian clock component PERIOD2 coordinates circadian output by interaction with nuclear receptors," *Genes and Development*, vol. 24, no. 4, pp. 345–357, 2010.

[34] H. Shirai, K. Oishi, T. Kudo, S. Shibata, and N. Ishida, "PPARα is a potential therapeutic target of drugs to treat circadian rhythm sleep disorders," *Biochemical and Biophysical Research Communications*, vol. 357, no. 3, pp. 679–682, 2007.

[35] K. Oishi, H. Shirai, and N. Ishida, "PPARα is involved in photoentrainment of the circadian clock," *NeuroReport*, vol. 19, no. 4, pp. 487–489, 2008.

[36] G. F. Gibbons, D. Patel, D. Wiggins, and B. L. Knight, "The functional efficiency of lipogenic and cholesterogenic gene expression in normal mice and in mice lacking the Peroxisomal Proliferator-Activated Receptor-alpha (PPAR-α)," *Advances in Enzyme Regulation*, vol. 42, pp. 227–247, 2002.

[37] D. D. Patel, B. L. Knight, D. Wiggins, S. M. Humphreys, and G. F. Gibbons, "Disturbances in the normal regulation of SREBP-sensitive genes in PPARα-deficient mice," *Journal of Lipid Research*, vol. 42, no. 3, pp. 328–337, 2001.

[38] S. Kersten, J. Seydoux, J. M. Peters, F. J. Gonzalez, B. Desvergne, and W. Wahli, "Peroxisome proliferator-activated receptor α mediates the adaptive response to fasting," *Journal of Clinical Investigation*, vol. 103, no. 11, pp. 1489–1498, 1999.

[39] J. Fu, G. Astarita, S. Gaetani et al., "Food intake regulates oleoylethanolamide formation and degradation in the proximal small intestine," *Journal of Biological Chemistry*, vol. 282, no. 2, pp. 1518–1528, 2007.

[40] J. Fu, S. Gaetani, F. Oveisi et al., "Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-α," *Nature*, vol. 425, no. 6953, pp. 90–93, 2003.

[41] P. M. Barger and D. P. Kelly, "PPAR signaling in the control of cardiac energy metabolism," *Trends in Cardiovascular Medicine*, vol. 10, no. 6, pp. 238–245, 2000.

[42] X. Wu, Z. Liu, G. Shi et al., "The circadian clock influences heart performance," *Journal of Biological Rhythms*, vol. 26, no. 5, pp. 402–411, 2011.

[43] G. Yang, Z. Jia, T. Aoyagi, D. McClain, R. M. Mortensen, and T. Yang, "Systemic PPARγ deletion impairs circadian rhythms of behavior and metabolism," *PLoS ONE*, vol. 7, no. 8, Article ID e38117, 2012.

[44] F. Anan, T. Masaki, N. Fukunaga et al., "Pioglitazone shift circadian rhythm of blood pressure from non-dipper to dipper type in type 2 diabetes mellitus," *European Journal of Clinical Investigation*, vol. 37, no. 9, pp. 709–714, 2007.

[45] C. Fontaine, G. Dubois, Y. Duguay et al., "The orphan nuclear receptor Rev-Erbα is a Peroxisome Proliferator-Activated Receptor (PPAR) γ target gene and promotes PPARγ-induced adipocyte differentiation," *Journal of Biological Chemistry*, vol. 278, no. 39, pp. 37672–37680, 2003.

[46] C. Liu, S. Li, T. Liu, J. Borjigin, and J. D. Lin, "Transcriptional coactivator PGC-1α integrates the mammalian clock and energy metabolism," *Nature*, vol. 447, no. 7143, pp. 477–481, 2007.

[47] M. Kawai, C. B. Green, B. Lecka-Czernik et al., "A circadian-regulated gene, Nocturnin, promotes adipogenesis by stimulating PPAR-γ nuclear translocation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 23, pp. 10508–10513, 2010.

[48] C. B. Green, N. Douris, S. Kojima et al., "Loss of Nocturnin, a circadian deadenylase, confers resistance to hepatic steatosis and diet-induced obesity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 23, pp. 9888–9893, 2007.

[49] Y. Nakahata, M. Akashi, D. Trcka, A. Yasuda, and T. Takumi, "The in vitro real-time oscillation monitoring system identifies potential entrainment factors for circadian clocks," *BMC Molecular Biology*, vol. 7, article 5, 2006.

[50] K.-D. Wagner and N. Wagner, "Peroxisome proliferator-activated receptor beta/delta (PPARβ/δ) acts as regulator of metabolism linked to multiple cellular functions," *Pharmacology and Therapeutics*, vol. 125, no. 3, pp. 423–435, 2010.

[51] G. Asher and U. Schibler, "Crosstalk between components of circadian and metabolic cycles in mammals," *Cell Metabolism*, vol. 13, no. 2, pp. 125–137, 2011.

[52] C. Esau, S. Davis, S. F. Murray et al., "miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting," *Cell Metabolism*, vol. 3, no. 2, pp. 87–98, 2006.

[53] D. Gatfield, G. Le Martelot, C. E. Vejnar et al., "Integration of microRNA miR-122 in hepatic circadian gene expression," *Genes and Development*, vol. 23, no. 11, pp. 1313–1326, 2009.

[54] E. Challet, I. Denis, V. Rochet et al., "The role of PPARβ/δ in the regulation of glutamatergic signaling in the hamster suprachiasmatic nucleus," *Cellular and Molecular Life Sciences*, vol. 70, no. 11, pp. 2003–2014, 2013.

[55] S. Liu, J. D. Brown, K. J. Stanya et al., "A diurnal serum lipid integrates hepatic lipogenesis and peripheral fatty acid use," *Nature*, vol. 502, no. 7472, pp. 550–554, 2013.

[56] P. McNamara, S.-B. Seo, R. D. Rudic, A. Sehgal, D. Chakravarti, and G. A. FitzGerald, "Regulation of CLOCK and MOP4 by nuclear hormone receptors in the vasculature: a humoral mechanism to reset a peripheral clock," *Cell*, vol. 105, no. 7, pp. 877–889, 2001.

[57] J. J. Hernandez-Morante, C. Gomez-Santos, F. Milagro et al., "Expression of cortisol metabolism-related genes shows circadian rhythmic patterns in human adipose tissue," *International Journal of Obesity*, vol. 33, no. 4, pp. 473–480, 2009.