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Review article

Rhythms of metabolism in adipose tissue and mitochondria

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ABSTRACT

Circadian clocks synchronize the daily functions of organisms with environmental cues like light-dark cycles and feeding rhythms. The master clock in the suprachiasmatic nucleus in the hypothalamus of the brain and the many clocks in the periphery are organized in a hierarchical manner; the master clock synchronizes the peripheral clocks, and the peripheral clocks provide feedback to the master clock in return. Not surprisingly, it has been shown that circadian rhythms and metabolism are closely linked. Metabolic disorders like obesity have a large cost to the individual and society and they are marked by adipose tissue and mitochondrial dysfunction. Mitochondria are central to energy metabolism and have key functions in processes like ATP production, oxidative phosphorylation, reactive oxygen species production and Ca^{2+} homeostasis. Mitochondria also play an important role in adipose tissue homeostasis and remodeling. Despite the extensive research investigating the link between circadian clock and metabolism, the circadian regulation of adipose tissue and mitochondria has mostly been unexplored until recently, and the emerging data in this topic are the focus of this review.

1. Introduction

The prevalence of metabolic disorders like obesity has been rising at alarming rates over the last several decades. According to a 2010 report (Hammond and Levine, 2010), more than two-thirds of the American population are overweight. In addition, obesity is also closely linked to many other diseases, such as hypertension, type 2 diabetes, coronary heart disease, stroke and several types of cancer, significantly adding to the economic cost of this epidemic to society (Hammond and Levine, 2010). Obesity is related to abnormalities in adipose tissue and mitochondrial dysfunction: normal energy metabolism requires an intricate balance of energy storage and energy dissipation via adipose tissue and mitochondrial function and in obesity this balance is tipped to favor triglyceride (TG) storage over lipid oxidation (Bjorndal et al., 2011).

Adipose tissue is a dynamic endocrine organ, central to whole-body energy homeostasis. In mammals, there are three types of adipose tissue: White adipose tissue (WAT), brown adipose tissue (BAT), and beige or brite adipose tissue (iBAT). WAT is involved in energy storage whereas BAT is responsible for energy dissipation in the form of heat through non-shivering thermogenesis. In addition to their opposite functions, BAT and WAT are also structurally quite different. WAT cells are spherical in shape and are composed of a single large lipid droplet along with a small number of mitochondria, whereas BAT cells are small and ellipsoid with multiple small lipid droplets and a large number of mitochondria (Cedikova et al., 2016; Harms and Seale, 2013). Beige adipocytes, on the other hand, have a mix of BAT and WAT characteristics both structurally and functionally, as they have more WAT-like properties at basal state, but they can acquire BAT-like thermogenic features upon activation of sympathetic nervous system by a stimulus like cold. Cold exposure is the predominant activator of BAT and the beiging of WAT in mammals, although it should be noted that in recent years exercise and irisin were also shown to activate these mechanisms (Virtanen, 2014). WAT is mainly located subcutaneously and viscerally and BAT is located in interscapular, cervical, axillary and perirenal space in mice. Human BAT is comprised of a mix of classical brown and beige adipocytes and these depots are in the cervical, supraclavicular, suprarenal and paravertebral regions.

Mitochondria have a vital role in energy metabolism and are essential for sustaining proper functioning of the complementary energy storage and energy dissipation functions that occur in the WAT and the BAT, respectively. Mitochondria are involved in lipolysis and lipogenesis, which are the major functions of WAT. In lipolysis, triglycerides are hydrolyzed from lipid droplets into glycerol and free fatty acids (FFA). These FFAs are then transferred into the mitochondria, either by diffusion or by carnitine shuttle for long-chain fatty acids. Consecutively, fatty acids are broken down into acetyl-CoA by β-oxidation in the mitochondrial matrix. Finally, acetyl-CoA is oxidized through the tricarboxylic acid cycle (TCA) and ATP is generated through oxidative phosphorylation by the electron transport chain (ETC). On the other hand, lipogenesis is the conversion of fatty acids to triglycerides for storage in the WAT as lipid droplets. Although

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lipogenesis occurs in the cytosol, the two important intermediates for lipogenesis; glycerol 3-phosphate and acetyl-CoA are generated in the mitochondria (Cedikova et al., 2016).

On the other end of the energetics spectrum, BAT mitochondria are essential for non-shivering thermogenesis. These specialized mitochondria have uncoupling protein 1 (UCP1) transported to their inner mitochondrial membrane, when activated by cold or by β-adrenergic (β-AR) stimulation. Upon stimulation, UCP1 uncouples the mitochondria by increasing the membrane conductance and dissipates the proton gradient required for ATP synthase function. This results in the energy of oxidized substrates being converted into heat rather than being used in ATP production. This whole process is called thermogenesis (Fedorenko et al., 2012).

In cases of metabolic imbalance as in obesity, excessive nutrient supply leads to high levels of glucose and FFAs in WAT and to accommodate this surplus, WAT expands and remodels itself. These adaptive responses include reduced mitochondrial number and function, reduced mitochondrial biogenesis, reduced OXPHOS and ATP production and increased amounts of ROS production, which results in dysfunctional hypertropic adipocytes. BAT activity on the other hand is thought to be counter-obesity, as increased BAT activity is linked to obesity-resistance in many mouse models. Additionally, in obese humans, lower mass and activity of UCP1-expressing adipocytes have been reported (reviewed in Cedikova et al., 2016).

The circadian clock is an important mediator of metabolism, which is also closely related to metabolic disorders like obesity (Brum et al., 2015; Karlsson et al., 2001; Lamia et al., 2008; Marcheva et al., 2010; Mukherji et al., 2015; Oishi et al., 2006; Rudic et al., 2004; Turek et al., 2005). Many organisms have an intrinsic clock, in order to adapt to the daily changes in the environment resulting from the 24-hour cycles of the Earth. In mammals, the intrinsic circadian system is composed of a central clock in the brain and many peripheral clocks organized in a hierarchical manner. The hypothalamic suprachiasmatic nucleus (SCN) contains the central clock, which is entrained mainly by light input and uses this information to synchronize the peripheral clocks. It should be noted that peripheral clocks can also be entrained via feeding or by humoral cues. At the molecular level, the core clock machinery is comprised of transcription/translation feedback loops, with the core elements CLOCK and BMAL1 activating transcription of *Period* (*Per*) and *Cryptochrome* (*Cry*) genes, the protein products of which form a complex that in turn represses the CLOCK:BMAL1 activity (reviewed in Green et al., 2008). Rhythmic *Bmal1* expression is further regulated by nuclear orphan receptors REV-ERB (consisting of REV-ERBα and REV-ERBβ) and retinoic acid receptor-related orphan receptors (RORs; consisting of RORα, RORβ and RORγ), which repress and activate the transcription of *Bmal1,* respectively. The circadian system exerts extensive regulation upon metabolic processes, but insight into how adipose tissue and mitochondria are regulated by the clock and how this impacts general metabolism has recently begun to emerge, and is the focus of this review.

2. Circadian regulation of adipose tissue and mitochondria

The regulation of energy homeostasis and metabolic function requires the orchestrated action of the SCN and the peripheral clocks. Adipose tissue is a key component of energy metabolism, and growing evidence supports its control by the circadian clock. Rhythmic expression of circadian clock genes have been characterized in adipose tissues by microarray and RNA-sequencing studies (Zhang et al., 2014; Zvonic et al., 2006). According to the murine circadian gene expression atlas, 8% of the protein-coding genes in BAT and 4% of the genes in WAT are rhythmic (Zhang et al., 2014). Some important functions of the adipose tissue, lipolysis and the release of free fatty acids (FFAs) and glycerol have also been reported to have diurnal rhythms (Shostak et al., 2013). These rhythms were altered in *Clock* mutant mice, along with decreased lipolysis, increased adiposity and increased sensitivity to fasting (Shostak et al., 2013). Interestingly, these animals were not able to maintain their body temperature following 12 hours of fasting, which could indicate impaired BAT thermogenesis. In order to identify the contribution of the adipocyte clocks per se in forming these metabolic phenotypes, conditional knockout mice that had an adipocyte-specific deletion of Bmal1 were used(Paschos et al., 2012). These mice developed obesity along with having reduced energy expenditure and altered food intake rhythms. They also had reduced polyunsaturated fatty acids in adipose tissue, plasma and hypothalamus. This FFA reduction in hypothalamus was inversely correlated with an increase in hypothalamic neuropeptides that regulate feeding activity, and was reversed by a polyunsaturated fatty-acid rich diet. This finding is interesting since it suggests bidirectional communication between hypothalamic feeding centers and adipocyte clocks. Thus, the adipocyte clock regulates the rhythmic fatty acid release into the circulation which in turn entrains the rhythmic feeding behavior. These studies are important in showing the importance of adipocyte clocks in metabolism, and how feedback from the peripheral clocks to the hypothalamus is required for maintaining energy homeostasis.

2.1. Circadian regulation of brown adipose tissue and thermogenesis

BAT is a specialized fat tissue, which is enriched in mitochondria and oxidative capacity and is known for its thermogenic properties. The discovery of brown fat is relatively new; its thermogenic properties were not known until the 1960s (Cannon and Nedergaard, 2004). More recently it became an exciting area of research, as its potential anti-obesity properties have been revealed (Feldmann et al., 2009; Kontani et al., 2005; Lowell et al., 1993; Saito et al., 2009). In mammals, upon cold exposure or food intake noradrenergic circuits are activated, which in turn activate BAT via UCP1, which uncouples the mitochondria and converts FFAs into heat. We previously mentioned the intricate link between the circadian clock and the adipose tissue. This section will focus on studies revealing the circadian control of brown fat and thermogenesis exclusively.

In addition to the activation of BAT by cold exposure, research suggests a concerted action between the SCN, ventromedial hypothalamus and the BAT clock, in order to achieve energy homeostasis fine-tuned to adapt to the daily environmental demands. Recent studies provided some mechanistic insight into the circadian regulation of brown fat thermogenesis. Core clock genes were induced upon cold-exposure in the BAT but not in the WAT, and this process is mediated by the β-adrenergic signaling and PGC1-α (Li et al., 2013). Paradoxically, *Bmal1* knockout mice did not have a defect in thermogenesis, despite having altered expression of genes involved in lipid metabolism and adaptive thermogenesis. A possible explanation for this contradictory finding could be that the circadian nuclear receptor REV-ERBα is a direct repressor of *Ucp1* (Gerhart-Hines et al., 2013). Wild type mice had reduced cold tolerance at ZT4-10, which is the peak of *Rev-erbα* (gene name *Nr1d1*) mRNA expression and this diurnal variation in cold sensitivity was abolished in the *Rev-erbα -/-* mice. Further, they showed that cold exposure rapidly down-regulates *Rev-erbα*, in parallel with an induction of *Ucp1*, and independent of noradrenergic stimulation. This study was important to establish how a circadian transcriptional repressor, REV-ERBα, integrates the circadian oscillators with the environmental demands in the BAT. This circadian regulation of *Ucp1* and thermogenesis could be serving the organism as an energy saving mechanism, where thermogenesis is repressed during sleep when mammals are not active.

The sleep/wake and fasting/feeding cycles are essential in the link between the circadian clock and metabolism. Disturbances in the time of feeding and shift work have metabolic consequences, as previously mentioned. The master clock in the SCN is mainly entrained by the light input whereas many peripheral clocks could be entrained by food intake (Green et al., 2008). How BAT is effected by this entrainment of the circadian clock by food and light input has been investigated. One

study showed that food entrained phase shifts of the circadian genes were significantly prolonged in the BAT from mice lacking the alpha isoform of perixosome proliferators-activated receptors *(Ppara-/-* mice*)* compared to wild-type mice (Goh et al., 2007), supporting a role for a food-entrainable circadian transcriptional regulator in BAT. Another study investigated the effects of time-restricted feeding of a high fat diet (HFD) on metabolic diseases (Hatori et al., 2012). One interesting finding from this study was that, compared to the ad lib HFD group, mice that were fed HFD time-restricted to their natural nocturnal feeding period had increased thermogenesis, improved nutrient utilization and reduced adiposity. Additionally, they had enhanced rhythmicity of the thermogenic genes and improved BAT morphology. A recent study by Orozco-Solis and colleagues provided mechanistic insight into how these environmental zeitgebers are integrated to circadian energetics in BAT (Orozco-Solis et al., 2016). Ventromedial hypothalamus (VMH) is thought to be involved in the regulation of food intake and metabolism. This study used a conditional knockout mouse model, that is lacking *Bmal1* specifically in the steroidogenic factor1 (SF1) neurons in the VMH, which are known to regulate diet-induced thermogenesis (Orozco-Solis et al., 2016). Disruption of the VMH clock in these mice resulted in increased energy expenditure and thermogenic capacity, despite having intact SCN and endogenous BAT clocks. These findings suggest that the VMH clock collects input from the environmental zeitgebers to modulate cyclic thermogenesis via adrenergic receptors, independent of the SCN and the endogenous BAT clock. Together with the previous studies, bidirectional communication between the adipocyte-hypothalamic axis clocks seems to be important to coordinate energy expenditure and feeding rhythms. These findings could also point to interesting therapeutic possibilities like time-restricted feeding or cold exposure as a means of facilitating thermogenic pathways (Fig. 1).

Light input entrains the circadian clocks through the information relay from the light sensitive ganglion cells in the retina to the master clock, SCN, which then synchronizes the peripheral clocks (Green et al., 2008). Disruption of the light-dark cycles such as occurs in jet-lag and shift work causes phase shifts and has been linked to metabolic disorders (Brum et al., 2015; Karlsson et al., 2001; Mukherji et al., 2015). This metabolic effect seems to be correlated with alterations in BAT function. It has been shown that advanced light phase shifts altered the circadian and thermogenic gene expression in BAT, as well as changing its morphology (Herrero et al., 2015). Another study investigated the effect of prolonged daily light exposure on adiposity and found that 24-hour light exposure increased adiposity by decreasing the intracellular adrenergic signaling and nutrient uptake in BAT (Kooijman et al., 2015). All these findings suggest an intricate balance between the environmental zeitgebers, the SCN, and other afferents in meeting the energy demands of the organism using brown fat thermogenesis.

The existence of brown adipose tissue in humans was not confirmed until the last decade (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). This relatively new finding created a lot of interest due to the potential therapeutic use of BAT activation in metabolic diseases. Activation of human brown fat via cold or β-adrenergic agonists has been shown to increase BAT metabolic activity and the resting metabolic rate (Cypess et al., 2015). A diurnal rhythm in glucose uptake in BAT has previously been shown in rodents in vivo with PET imaging (van der Veen et al., 2012). In a recent study, in vivo, in vitro and ex vivo experiments with human BAT showed consistencies with rodent data (Lee et al., 2016). The study revealed a thermogenic circadian rhythm in human BAT, that is glucose responsive. It has also demonstrated circadian rhythmicity of *Ucp1*, *Glut4* and *Rev-erbα*, in both differentiated human brown adipocytes and human BAT explants. The glucose rhythms in patients showed greater fluctuations in patients with less BAT abundance, which might suggest that BAT acts as a buffer for glycemia. Although more studies to confirm this correlation are needed, this potential glucose-modulatory role of BAT in humans could lead to new therapeutic approaches in treating hyperglycemia and diabetes.

2.2. Circadian control of oxidation and nutrient utilization

Mitochondria are critical hubs for energy metabolism and homeostasis in eukaryotic cells. Originally evolved from a prokaryotic ancestor, mitochondria produce more than 95% of the ATP that is required for the cellular processes (Cedikova et al., 2016). In addition to its main function, which is synthesizing ATP through oxidative phosphorylation, mitochondria also contribute to energy homeostasis in many other ways, including facilitation of lipolysis through fatty acid oxidation, contributing to maintenance of Ca^{2+} homeostasis, and regulation of apoptosis via reactive oxygen species (ROS) production (Cedikova et al., 2016; Vakifahmetoglu-Norberg et al., 2017). Considering the dynamic nature of mitochondria, which adapt to the metabolic needs of the cell, it is not surprising that a strong link between the circadian clock and the mitochondrial function exists.

Rhythmic food intake is one of the central clock outputs and is known to have a profound effect on metabolism. Nutrient status is critical in determining the temporal regulation of mitochondrial function as it provides the oxidizable substrates for the electron transport chain and oxidative phosphorylation. It was unclear, though, if the oxidation of these substrates in the mitochondria has self-sustained rhythms. Previously it has been reported that nicotinamide phosphoribosyltransferase (NAMPT), the rate limiting enzyme for NAD^+ biosynthesis, is under direct control of the circadian clock, which results in rhythmic NAD^+ levels (Nakahata et al., 2009). More recently, Peek and colleagues found that these rhythmic NAD^+ levels are coupled by rhythms in fatty acid oxidation and mitochondrial respiration. Most importantly, they showed that these NAD^+-dependent rhythms are self-sustained (Peek CB et al., 2013). Thus, the rhythms persisted even under constant nutrient status. Supporting that these rhythms are governed by the circadian clock, the study reported reduced mitochondrial NAD^+ and fatty acid oxidation levels in livers from fasted animals *Bmal1 -/-* mice. Proteomics on isolated mouse liver mitochondria from another study revealed that 38% of the mitochondrial proteins oscillate diurnally, providing additional evidence to the circadian control of mitochondrial function (Neufeld-Cohen et al., 2016). Notably, a number of rate-limiting enzymes that are critical for mitochondrial metabolic pathways showed diurnal oscillations. One of those rhythmic enzymes was carnitine palmitoyltransferase 1 (CPT1), which is critical for the transport of long-chain fatty acids through the carnitine shuttle for fatty acid oxidation. Collectively, these studies reveal circadian control of nutrient utilization and mitochondrial oxidative metabolism. The self-sustained metabolic rhythms are a possible adaptation to the daily activity and rest cycles as they let the organism be most efficient energetically by making metabolic activity peak just before the period that mice are most active.

2.3. Rhythmic post-translational modifications of mitochondrial proteins

Circadian rhythms in the absence of transcription have been reported in a eukaryote (O'Neill et al., 2011; Woolum, 1991), which might point to post-translational mechanisms in the regulation of the circadian clock. In support of this, there is a mismatch between the percent of oscillating transcripts and oscillating proteins from mouse liver, with almost 2-fold more oscillating proteins than transcripts (Mauvoisin et al., 2014; Reddy et al., 2006; Robles et al., 2014). Interestingly, there is also a discrepancy between the cycling mitochondrial proteome and transcriptome (Neufeld-Cohen et al., 2016). A number of studies reported circadian regulation of mitochondria via rhythmic acetylation. One mass spectrometry based study analyzed genome-wide lysine acetylation in wild type and *Clock-/-* mice livers and revealed clock-driven acetylation in a number of mitochondrial proteins that are involved in metabolic pathways (Masri S et al., 2013). Regulation of fatty acid oxidation by NAD^+-dependent deacetylase

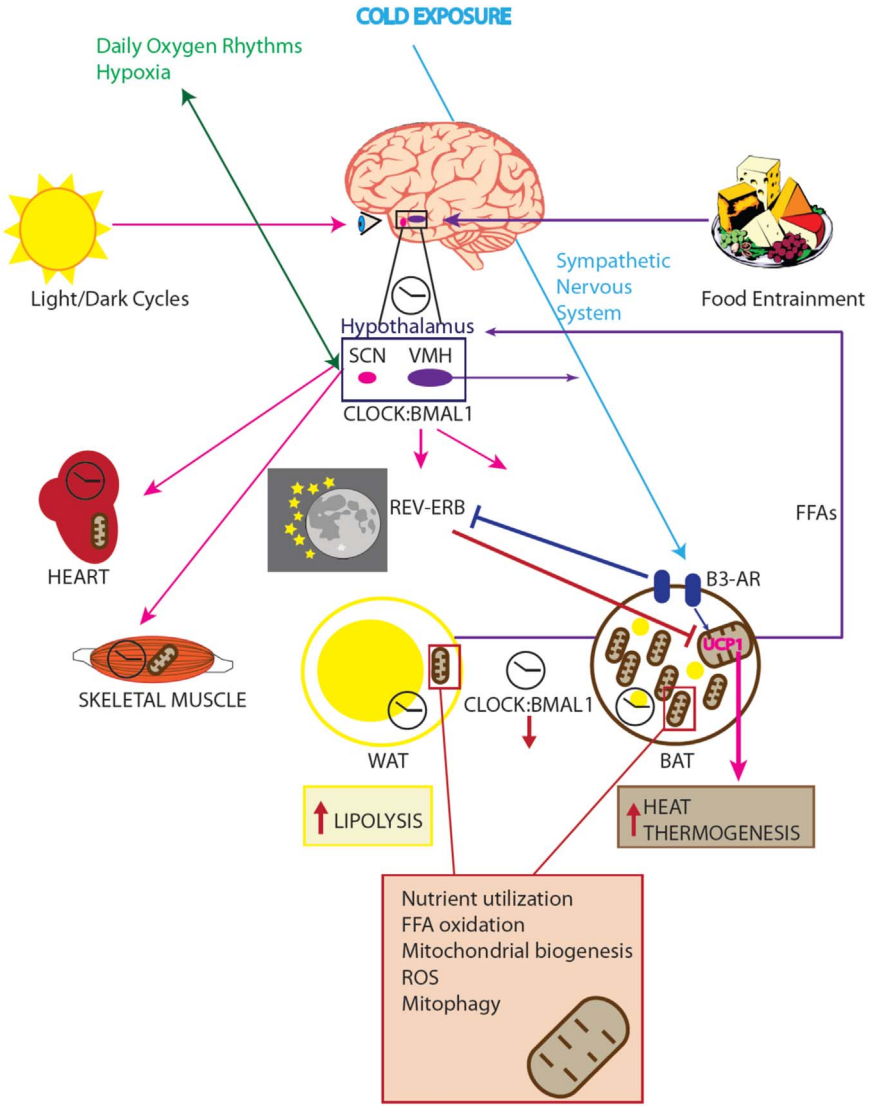

Fig. 1. The Circadian System as a Mediator of Metabolic Functions in Different Tissues. Circadian clock synchronizes the input from the external zeitgebers like light or food with the cell-autonomous peripheral clocks in different tissues. These peripheral clocks also provide feedback to the master clock, forming a feedback loop. Metabolic functions in the tissues with high energy demand like heart, BAT and skeletal muscle are modulated by the circadian clock.

SIRT3 has previously been shown (Hirschey et al., 2010). Circadian control of this process has been revealed by Peek and colleagues, where they showed *Bmal1*-dependent deacetylation of mitochondrial proteins via SIRT3 (Peek CB et al., 2013). Additionally, a more recent study showed rhythmic complex I activity along with rhythmic acetylation of complex I (Cela et al., 2016). These studies suggest a role for post-translational modifications in circadian time-keeping, particularly in the mitochondria.

2.4. Circadian control of ROS and hypoxia

O_2 radicals that are byproducts of mitochondrial oxidative phosphorylation form ROS, to which the cell responds by activating damage-control mechanisms such as autophagy. The ratio of oxidative stress to antioxidant mechanisms is critical for cellular homeostasis and if the oxidative damage is too high the cell could undergo apoptosis. Excess levels of ROS have been linked to aging. (Vakifahmetoglu-Norberg et al., 2017). Research has suggested links between the circadian clock and oxidative stress. *Bmal1*-/- mice were reported to have increased ROS levels in a number of tissues, along with reduced lifespan and various other symptoms of premature aging (Kondratov et al., 2006). Yet it was not clear in this study whether the effect of *Bmal1* on ROS levels is direct, or rather it is secondary to other aging symptoms and metabolic stresses. Other studies reported reduced cycling of clock genes in response to oxidative stress in *Drosophila* (Zheng et al., 2007) and increased resistance to the cytotoxic effects of ROS in *Per2* mutant mouse embryonic fibroblasts (Magnone et al., 2014). A more recent study investigated liver-specific *Bmal1* knockout mice and reported morphological alterations in their mitochondria along with reduced respiration and increased oxidative stress (Jacobi D et al., 2015). Remarkably, these mice lacked the normal diurnal mitochondrial remodeling through the mitochondrial dynamic fusion/fission processes. As previously mentioned, antioxidant mechanisms are critical for the cell to balance out the oxidative stress. Thus, mitochondria actively scavenge H_2O_2 through some antioxidant mechanisms such as peroxiredoxins. Circadian oscillations have been reported in hyperoxidized 2-Cys peroxiredoxin III (PrxIII-SO_3) and sulfiredoxin, which reverses its hyperoxidation (Kil et al., 2012; Kil IS et al., 2015). All these studies suggest a role for the circadian clock to protect against premature aging by maintaining the balance between oxidative stress and antioxidant mechanisms.

Oxygen is critical for aerobic mitochondrial function and low-oxygen levels trigger critical cellular adaptations with the induction of hypoxia-inducible factors (HIFs) (Solaini et al., 2010). Daily rhythms in

oxygen consumption and blood oxygenation of mice have recently been reported (Adamovich et al., 2017). Remarkably, oxygen rhythms were sufficient to reset the circadian clocks in cultured cells in a HIF1α-dependent fashion. Crosstalk between hypoxia signaling and the circadian clock has also been reported in the liver, heart (Wu et al., 2017) and in skeletal muscle (Peek et al., 2017). Reduced mitochondrial volume and respiration was previously shown in skeletal muscle from *Clock∆19* mutant and *Bmal1-/-* mice (Andrews JL et al., 2010). In skeletal myotubes, CRISPR-mediated deletion of *Bmal1* altered the induction of HIF1α in response to hypoxia (Peek et al., 2017). Conversely, deletion of the genes encoding the clock repressors CRY1 and CRY2 further stabilized HIF1α levels. Furthermore, induction of HIF1α and clock-dependent transcription in response to strenuous exercise showed time-of-day variation. Lastly, in a mouse model of heart attack, *Per1-/-;Per2-/-* mice were more vulnerable to the hypoxia-induced damaging effects of the heart attack, suggesting a protective role for the circadian clock in protection from hypoxia-induced cell death (Wu et al., 2017).

Collectively, these studies suggest an intricate link between circadian clocks and the metabolic flexibility of mitochondria in response to oxidative stress and hypoxia. Dynamic regulation of mitochondria through biogenesis and mitophagy is critical in adipose tissue remodeling. Thus, WAT could acquire “brown-like” thermogenic properties upon β3-adrenergic (β3-AR) stimulation via mitochondrial biogenesis, and would go back to being “white-like” via mitophagy upon withdrawal of the stimulus (Altshuler-Keylin and Kajimura, 2017). Whether this mitochondrial flexibility in adipose tissue is affected by the circadian clocks is to be investigated. Interestingly, there is a discrepancy between the adipose tissue phenotypes in animals that lack different autophagy-related genes (Altshuler-Keylin and Kajimura, 2017). While the deletion of many autophagy genes resulted in the induction of WAT browning, as expected, deletion of p62 resulted in an opposite obesity phenotype. Interestingly, p62 is involved in many signaling pathways, including Nrf2, which was recently shown to connect redox oscillations to circadian transcriptional rhythms (Rey et al., 2016). More studies are needed to investigate the link between the circadian clock and mitochondrial remodeling in the adipose tissue.

2.5. Rhythmic Ca^{2+} homeostasis and the mitochondria

Ca^{2+} is essential for mitochondrial function and homeostasis. Circadian rhythms in cytosolic Ca^{2+} in SCN neurons have previously been reported (Ikeda et al., 2003), and these rhythms were found to be dependent on *Bmal1* (Ikeda and Ikeda, 2014). On the other hand, circadian clock and calcium signaling-mediated oscillations of ATP release in astrocytes have also been reported (Marpegan et al., 2011). Burkeen and colleagues reported mitochondrial Ca^{2+} rhythms in SCN astrocytes, and these rhythms were in phase with ATP rhythms and in antiphase with cytosolic Ca^{2+} rhythms (Burkeen et al., 2011). Furthermore, pharmacological inhibition of mitochondrial Ca^{2+} uniporter was sufficient to alter the rhythmic ATP accumulation. Together, these results suggest an important role for circadian mitochondrial Ca^{2+} rhythms in rhythmic ATP accumulation in the astrocytes.

3. Therapeutic opportunities

With increasing research revealing an overlap between the circadian dysfunction and metabolic disorders, attention has been focused on identifying small molecules to modulate the circadian clock. The nuclear orphan receptors REV-ERBs and RORs have been the main focus as the drug targets, and in vitro and in vivo studies with ligands modifying these receptors showed promise in potentially alleviating metabolic disorders. Other circadian drug targets include, casein kinase 1 (CK1s; consisting of CK1ε and CK1δ), which is a negative regulator of PER proteins and the NAD^+-dependent deacetylase Sirtuin1 (SIRT1), which also modulates the CLOCK (Schroeder and Colwell, 2013).

Given the diverse roles of REV-ERB in modulating metabolism, it is not surprising that many studies focused on REV-ERB as a drug target. REV-ERB and ROR have opposite regulatory functions on *Bmal1* expression as previously stated. REV-ERB is thought to have a bidirectional role on adipogenesis, since there is a discrepancy between the in vitro and in vivo data (Kojetin and Burris, 2014). Treatment of 3T3-L1 cells with a synthetic REV-ERB agonist induced adipogenesis in vitro (Kumar et al., 2010). Conversely, *Rev-erbα -/-* mice had increased weight gain and adiposity during a high-fat diet challenge (Delezie et al., 2012). Another study has shown that the degradation of REV-ERBα is required for the later stages of adipocyte differentiation, which might explain this discrepancy (Wang and Lazar, 2008). On the other hand, *Rora* mutant “staggerer” ($Rora^{sg/sg}$) mice has the opposite phenotype where it is resistant to diet-induced obesity, as might be expected. These mice also showed some deficits in thermogenic function (Bertin et al., 1990; Lau et al., 2008). Considering the modulatory role of REV-ERBα on cold-induced BAT thermogenesis, it will be of interest to investigate whether ROR or REV-ERBα ligands manifest any of their metabolic effects via alterations in BAT function.

REV-ERB agonists were investigated for their effects on the circadian clock and metabolism. The first published synthetic REV-ERB agonist had a phase-resetting role on the peripheral lung clocks (Meng et al., 2008). Other REV-ERB agonists altered circadian behavior and core clock gene expression in vivo (Solt et al., 2012). Notably, these agonists (SR9011 and SR9009) also had a profound effect on metabolism. Mice treated with the agonists had reduced weight and fat mass along with increased oxygen consumption. REV-ERB ligands also differentially affected the rhythmic expression patterns of the metabolic genes in the liver, skeletal muscle and adipose tissue. Thus, in skeletal muscle, the circadian rhythms for fatty acid oxidation and glycolysis related genes were amplified, whereas in the adipose tissue the circadian rhythms for lipid storage genes were attenuated. Furthermore, the agonists improved the metabolic profile in obese mice, with decreased fat and plasma lipids and increased weight loss in the drug-injected group, compared to the vehicle-injected group. Consistent with these findings, Woldt and colleagues showed that REV-ERBα modulates skeletal muscle oxidative capacity and overexpression or pharmacological activation of *Rev-erbα* improves mitochondrial number and function as well as exercise capacity (Woldt et al., 2013). These results altogether are promising as they might have implications for treating metabolic diseases in humans.

Another therapeutic strategy for modulating metabolism has been the ligand modulation of RORs. In contrast to REV-ERBs, RORs enhance *Bmal1* expression. As might be expected from their opposite role in circadian gene expression, REVERBs and RORs seem to regulate metabolic function in opposing ways. For instance, *Rora* staggerer ($Rora^{sg/sg}$) mice are resistant to diet-induced obesity (Lau et al., 2008). Interestingly, RORγ inhibits adipogenesis *in vitro*, yet *Rorc -/-* mice have increased adipocyte formation in vivo (Meissburger et al., 2011). On the other hand, these animals were protected against diet-induced hyperglycemia and had improved insulin sensitivity. The discrepancy with the *in vitro* and *in vivo* adipogenesis data might indicate a bidirectional function for ROR in adipogenesis, similar to REV-ERB. Thus, ligand modulation of RORs seems to support that bidirectional role. Based on its in vivo effects on metabolism, most of the initial efforts focused on suppressing ROR activity (Kojetin and Burris, 2014). Accordingly, RORγ-specific inverse agonist SR1555 had anti-obesity effects when administered to obese mice in vivo, yet also causing a reduction in food intake (Chang et al., 2015). Thus it was not clear if the anti-obesity effects were linked to the reduced food intake. Interestingly, they also showed an induction of thermogenic genes in BAT in this study, in mice treated with the compound. On the other hand, a recent high-throughput small molecule screen identified Nobiletin, an agonist for RORs, as a protector against metabolic syndrome (He et al., 2016). Mice treated with Nobiletin had robust resistance to diet-induced obesity despite having similar food intake as the vehicle treated mice. These

mice also had reduced fat mass, increased locomotor activity and oxygen consumption along with improved glucose and lipid homeostasis. Notably, these effects were clock-dependent, as Nobiletin treatment had no beneficial effects in the *Clock* mutant mice. Moreover, Nobiletin was protective against metabolic syndrome in a mouse model of type 2 diabetes (*db/db*). These studies altogether suggest a complex and dual role for ROR function. This is not surprising considering RORs have been shown to regulate the expression of several key metabolic genes. For instance, RORα regulates FGF21, a key metabolic hormone (Wang et al., 2010). Moreover, in skeletal muscle, RORα has been shown to regulate *caveolin-3* and *cpt-1*, which are critical for lipid metabolism and fatty acid oxidation (Lau et al., 2004). To summarize, the diverse functions of RORs and REV-ERBs on different metabolic pathways could explain their dual function on metabolism. It would be interesting to see if REV-ERB antagonists would have a beneficial metabolic role in a similar fashion, especially considering REV-ERB's role on modulating BAT thermogenesis as a repressor of *Ucp1*.

Other pharmacological efforts to modulate the circadian clock focused on targeting CK1, CRY and SIRT1. Pharmacological activation of the NAD^+-dependent deacetylase SIRT1, dampened the circadian gene expression in vitro and in vivo (Bellet et al., 2013). Another study showed reduced *Sirt1* expression along with reduced *Nampt*, *Clock* and *Bmal1* expression in the WAT of *db/db* obese mice. Interestingly, a common diabetes drug, Metformin, restored the *Sirt1*, *Nampt*, *Clock* and *Bmal1* expression levels in the WAT of these mice (Caton et al., 2011). Metformin is also known to shorten the period length, via CK1ε-dependent degradation of PER2 (Um et al., 2007). On the other hand, inhibition of CK1δ was shown to lengthen the period and was able to restore perturbed circadian behavior (Meng et al., 2010). Thus CKδ inhibitors could hold potential to alleviate circadian disruptions in shift workers. Small molecule modulators of CRY proteins have also been identified and could hold promise for diabetes treatment (Hirota et al., 2012; Humphries et al., 2016). Overall, more studies are needed to show metabolic improvements in vivo by pharmacologically targeting these genes.

4. Conclusions

Collectively, emerging evidence in the last couple decades suggests substantial crosstalk between the circadian clock and the dynamic metabolic functions of peripheral tissues and mitochondria. The challenge of understanding how circadian clocks affect metabolism in peripheral tissues and to develop targeted therapeutics is the complexity of the system, as the system is comprised of cell-autonomous clocks that are also regulated by systemic cues and the central clock, and many key core clock genes and proteins are involved in multiple signaling pathways. Thus, the discrepancy between the in vitro and in vivo adipogenesis data supports this notion. Additionally, most of the studies regarding adipose tissue gathered data from the adipocyte-specific conditional knockout mice, which does not differentiate between WAT and BAT. WAT- and BAT-specific knockout mice are needed to identify the different mechanisms circadian clock affects the two organs.

Conflict of Interest

None.

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