

Rev-erbs: Integrating Metabolism Around the Clock

Mitchell A. Lazar

Abstract Mammalian circadian and metabolic physiologies are intertwined, and the nuclear Rev-erb α is a key transcriptional link between them. Rev-erb α , and the highly related Rev-erb β , are potent transcriptional repressors that are required for the function of the core mammalian molecular clock. The Rev-erbs are also critical regulators of clock output in metabolic cells and tissues. This chapter focuses on the physiological functions of Rev-erb α and β in regulating circadian rhythms and metabolism in mammalian tissues.

Introduction

Much of biology is conducted with rhythms that have a phase of approximately 24 h, matching the duration of a day on planet Earth (Huang et al. 2011). The genetic basis of these circadian rhythms was unveiled in the fruit fly, *Drosophila melanogaster*, where the clock mechanism involves feedback regulation by factors whose own expression exhibit circadian rhythmicity (Rosbash et al. 1996). These factors function as transcriptional regulators, and it is now recognized that most genomes, including those of all mammals that have been evaluated, are transcribed in a rhythmic manner (Schibler 2006).

The mammalian clock mechanism involves interconnected transcriptional and translational feedback loops, where the most well-understood positive regulator is a heterodimer of the basic helix-loop-helix (HLH) transcription factors BMAL1 and CLOCK (King and Takahashi 2000). In addition to positively regulating clock output genes, the BMAL1/CLOCK heterodimer activates the expression of two negative regulators. One is another bHLH heterodimer, comprised of the proteins PERIOD (PER) and CRYPTOCHROME (CRY), which interact with BMAL1/CLOCK to

M.A. Lazar, M.D., Ph.D. (✉)

Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Department of Genetics, and The Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA
e-mail: lazar@mail.med.upenn.edu

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interfere with its activity (King and Takahashi 2000). The second repressive loop is mediated by the Rev-erb nuclear receptors (NRs) α and β , of which Rev-erb α is the more highly functional (Everett and Lazar 2014). This chapter will focus on the Rev-erbs, particularly on the more well-studied Rev-erb α .

Repression of Transcription by Rev-erbs

Rev-erbs belong to a large NR superfamily of ligand-regulated transcription factors (Evans 2013). Discovered in 1989 (Lazar et al. 1989; Miyajima et al. 1989), Rev-erb α was one of the first identified orphan NRs, i.e., a member of the family whose ligand was not predicted from earlier physiology and biochemical studies (Mullican et al. 2013). The highly related Rev-erb β was identified in 1994 (Bonnelye et al. 1994; Dumas et al. 1994; Forman et al. 1994; Retnakaran et al. 1994). Molecular heme has been identified as the endogenous ligand for Rev-erb α and Rev-erb β (Raghuram et al. 2007; Yin et al. 2007). Although the physiological function of this regulation is not well understood, the ability to sense heme levels may position Rev-erb as a mediator of metabolic effects on metabolism.

Rev-erbs bind sequence-specifically to DNA, with the preferred binding site consisting of the classical NR half-site AGGTCA flanked by an A/T-rich 5' sequence (Harding and Lazar 1993). This binding site is referred to as the RevRE or as the RORE, as it is also bound by the Retinoic Acid Receptor-related Orphan Receptor (ROR; Giguere et al. 1994). The DNA-binding domain (DBD) of Rev-erb α binds in the major groove of the AGGTCA half-site, whereas a C-terminal extension makes minor groove contacts with the A/T-rich 5' sequence (Zhao et al. 1998). Rev-erbs bind as a monomer to this site but bind even more tightly as a dimer to a direct repeat with a 2 base pair spacer, referred to as the RevDR2 (Harding and Lazar 1995).

Rev-erbs lack the C-terminal region that is required for ligand-dependent transcriptional activation by other NRs (Glass and Rosenfeld 2000). Thus, they function primarily as potent repressors of transcription when bound to DNA (Zamir et al. 1997), interacting constitutively with the Nuclear Corepressor 1 (NCoR; Horlein et al. 1995; Zamir et al. 1996). NCoR is a large protein (~270 kDa) with inherent repressive function as well as several short helical domains that specifically interact with NRs, called the corepressor-NR (CoRNR) boxes (Hu and Lazar 1999). Heme further stabilizes its interaction with full-length, endogenous NCoR (Raghuram et al. 2007; Yin et al. 2007). In addition to serving as a heme sensor, the Rev-erb activity may also be sensitive to the oxidation state of the heme iron (Marvin et al. 2009). To bind NCoR stably enough to actively repress transcription, two Rev-erb α molecules must interact with CoRNR peptides from NCoR; this interaction can occur at the RevDR2 site, which the Rev-erbs bind cooperatively as a dimer, or at two RevRE/RORE sites bound independently by Rev-erb monomers (Zamir et al. 1997).

NCoR represses transcription by nucleating a large multiprotein repressor complex, which impacts the epigenome and the function of core transcriptional factors and RNA polymerase II (Guenther et al. 2000; Yoon et al. 2003). Stoichiometric components of the NCoR complex include Transducin Beta-Like 1 (TBL1), G-protein Pathway Suppressor 2 (GPS2), and Histone Deacetylase 3 (HDAC3; Guenther et al. 2000; Zhang et al. 2002; Yoon et al. 2003). HDAC3 is of particular interest, because it is an epigenomic modulator that deacetylates lysine residues in the tails of nucleosomal histone proteins to create a repressive chromatin environment (Haberland et al. 2009). NCoR and HDAC3 are both required for Rev-erb α to repress *Bmal1* gene transcription (Yin and Lazar 2005), and both NCoR and HDAC3 are associated with Rev-erb α at thousands of DNA binding sites genome wide in the mouse liver (Feng et al. 2011).

Circadian Biology of Rev-erbs

In 1998, Rev-erb α was noted to one of the genes that oscillates within the circadian transcriptome of mammalian cells cycling in tissue culture (Balsalobre et al. 1998). In mice Rev-erb α mRNA expression is robustly circadian in multiple tissues (Yang et al. 2006), and genetic deletion of Rev-erb α shortens the period of behavioral rhythms by ~30 min in the absence of daily light cues (Preitner et al. 2002). Rev-erb α modulates the rhythmicity of additional circadian regulators, including *Clock* (Crumbley and Burris 2011), *Cry1* (Ukai-Tadenuma et al. 2011), *Nfil3/E4Bp4* (Duez et al. 2008), and *Npas2* (Crumbley et al. 2010) and thus has a major influence on the cell-autonomous molecular timing system. Indeed, constitutive expression of Rev-erb α in mouse liver represses the majority of cycling transcripts (Kornmann et al. 2006). Importantly, ablation of both Rev-erb α and β abrogates circadian gene expression in mouse embryonic fibroblasts, demonstrating a fundamental requirement for the Rev-erbs (Bugge et al. 2012). Moreover, genetic mutation of Rev-erb α and β caused arrhythmic behavior in mice (Cho et al. 2012). Therefore Rev-erb α and β are both required components of the core clock machinery. Loss of either Rev-erb alone is insufficient to abolish circadian rhythms, indicating that their clock functions are redundant, although Rev-erb α is more critical because its absence modestly disrupts normal circadian rhythms whereas the loss of Rev-erb β does not.

Rev-erb α and Metabolism

Circadian rhythms and metabolism are highly intertwined (Eckel-Mahan and Sassone-Corsi 2013), and indeed Rev-erb α regulates metabolic function in many tissues. In the liver, Rev-erb α regulates cholesterol and bile acid metabolism (Duez et al. 2008; Le Martelot et al. 2009), and more recently has been observed to play a

key role in the circadian regulation of triglyceride metabolism (Feng et al. 2011). Rev-erb α binds widely and robustly to the genome at ZT10, when its expression is maximal; however, it binds to very few sites when its expression is at a nadir, such as at ZT22. This genomic binding is enriched at genes involved in lipid metabolism and, indeed, mice lacking Rev-erb α have mild fatty liver, or hepatic steatosis (Feng et al. 2011). The oscillatory expression of Rev-erb α regulates circadian gene expression directly at target genes with strong binding motifs, whose circadian expression is antiphase to that of Rev-erb α , as well as indirectly by repression of another circadian repressor called E4BP4, whose target genes are expressed in phase with Rev-erb α (Fang et al. 2014). The liver cistrome of Rev-erb β is quite similar, and knockdown of Rev-erb β in livers of Rev-erb α null mice caused a more markedly fatty liver (Bugge et al. 2012). NCoR and HDAC3 bind to the genome at the vast majority of Rev-erb sites and, indeed, ablation of either NCoR or HDAC3 in mouse liver leads to marked hepatic steatosis (Knutson et al. 2008; Sun et al. 2012, 2013).

Studies of adipocyte differentiation in cultured cell lines have suggested that Rev-erb α plays an important role in adipocyte differentiation (Chawla and Lazar 1993; Fontaine et al. 2003; Wang and Lazar 2008), yet white adipose tissue (WAT) mass was not reduced in mice lacking Rev-erb α (Chomez et al. 2000; Delezie et al. 2012), indicating that Rev-erb α is not absolutely required for adipocyte formation *in vivo*. Rev-erb α may play a role in brown adipose tissue (BAT), which is a major site of thermogenesis (Gerhart-Hines et al. 2013). Circadian expression of Rev-erb α in BAT peaks at ZT10, which is antiphase to the circadian rhythm of body temperature. Mice lacking Rev-erb α have a higher nadir in body temperature, at least in part due to derepression of Uncoupling Protein 1 (UCP1), which is a circadian target of Rev-erb α and constitutively high in the BAT of mice genetically lacking Rev-erb α (Gerhart-Hines et al. 2013). Mice also have an increased vulnerability to cold temperature at times of day when Rev-erb α levels are high; this vulnerability is ameliorated in the absence Rev-erb α (Gerhart-Hines et al. 2013).

A role for Rev-erb α in skeletal myocytes was first identified in C2C12 cultured myoblasts, where Rev-erb α represses the expression of genes involved in muscle cell differentiation (Downes et al. 1995). Rev-erb α mRNA expression is circadian manner in mouse skeletal muscle (Yang et al. 2006), and loss of Rev-erb α function reduces mitochondrial content and function, leading to an impaired exercise capacity (Woldt et al. 2013). It should be noted that the transcriptomic changes in muscle are not observed in liver or BAT and thus reflect tissue-specific functions of Rev-erb α .

Rev-erb α is also expressed in a circadian manner in the pancreatic islets and plays a role in the function of insulin-producing β -cells and glucagon-producing α -cells (Vieira et al. 2012, 2013). Islets isolated at the peak of Rev-erb α expression have higher levels of glucose-stimulated insulin secretion (Vieira et al. 2012), and Rev-erb α also promotes glucagon secretion in α -cells of the pancreas (Vieira et al. 2013).

Inflammatory cells are increasingly linked to metabolic function (Osborn and Olefsky 2012), and Rev-erb α mediates the circadian gating of the LPS-induced endotoxic response (Gibbs et al. 2012). Genome-wide studies of Rev-erb α and Rev-erb β cistromes and transcriptomes suggest that Rev-erb α influences macrophage gene expression at bindings sites marked by hematopoietic transcription factors, including PU.1 (Lam et al. 2013).

Conclusions

The nuclear receptor Rev-erb α acts in a tissue-specific manner to regulate circadian rhythms as well as metabolism, in some cases acting redundantly with Rev-erb β . A critical question is whether Rev-erb α can be targeted for therapeutic purposes. Synthetic pharmacological agonists have been developed (Grant et al. 2010; Solt et al. 2012), yet the tissue-specific complexity of Rev-erb biology raises major challenges to human therapeutics. Perhaps the dramatic circadian expression of Rev-erbs can be exploited by timing drug delivery to selectively impact their specific and beneficial functions in integration of metabolism and the circadian clock.

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