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-erbα is the more highly functional (Everett and Lazar 2014). This chapter will focus on the Rev-erbs, particularly on the more well-studied Rev-erbα.

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-erbα 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-erbβ 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-erbα and Rev-erbβ (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-erbα 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-erbα 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-erbα to repress *Bmal1* gene transcription (Yin and Lazar 2005), and both NCoR and HDAC3 are associated with Rev-erbα at thousands of DNA binding sites genome wide in the mouse liver (Feng et al. 2011).

Circadian Biology of Rev-erbs

In 1998, Rev-erbα 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-erbα mRNA expression is robustly circadian in multiple tissues (Yang et al. 2006), and genetic deletion of Rev-erbα shortens the period of behavioral rhythms by ~30 min in the absence of daily light cues (Preitner et al. 2002). Rev-erbα 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-erbα in mouse liver represses the majority of cycling transcripts (Kornmann et al. 2006). Importantly, ablation of both Rev-erbα 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-erbα and β caused arrhythmic behavior in mice (Cho et al. 2012). Therefore Rev-erbα 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-erbα is more critical because its absence modestly disrupts normal circadian rhythms whereas the loss of Rev-erbβ does not.

Rev-erbα and Metabolism

Circadian rhythms and metabolism are highly intertwined (Eckel-Mahan and Sassone-Corsi 2013), and indeed Rev-erbα regulates metabolic function in many tissues. In the liver, Rev-erbα 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-erbα 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-erbα have mild fatty liver, or hepatic steatosis (Feng et al. 2011). The oscillatory expression of Rev-erbα regulates circadian gene expression directly at target genes with strong binding motifs, whose circadian expression is antiphase to that of Rev-erbα, as well as indirectly by repression of another circadian repressor called E4BP4, whose target genes are expressed in phase with Rev-erbα (Fang et al. 2014). The liver cistrome of Rev-erbβ is quite similar, and knockdown of Rev-erbβ in livers of Rev-erbα 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-erbα 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-erbα (Chomez et al. 2000; Delezie et al. 2012), indicating that Rev-erbα is not absolutely required for adipocyte formation in vivo. Rev-erbα 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-erbα in BAT peaks at ZT10, which is antiphase to the circadian rhythm of body temperature. Mice lacking Rev-erbα 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-erbα and constitutively high in the BAT of mice genetically lacking Rev-erbα (Gerhart-Hines et al. 2013). Mice also have an increased vulnerability to cold temperature at times of day when Rev-erbα levels are high; this vulnerability is ameliorated in the absence Rev-erbα (Gerhart-Hines et al. 2013).

A role for Rev-erbα in skeletal myocytes was first identified in C2C12 cultured myoblasts, where Rev-erbα represses the expression of genes involved in muscle cell differentiation (Downes et al. 1995). Rev-erbα mRNA expression is circadian manner in mouse skeletal muscle (Yang et al. 2006), and loss of Rev-erbα 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-erbα.

Rev-erbα 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-erbα expression have higher levels of glucose-stimulated insulin secretion (Vieira et al. 2012), and Rev-erbα 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-erbα mediates the circadian gating of the LPS-induced endotoxic response (Gibbs et al. 2012). Genome-wide studies of Rev-erbα and Rev-erbβ cistromes and transcriptomes suggest that Rev-erbα influences macrophage gene expression at bindings sites marked by hematopoietic transcription factors, including PU.1 (Lam et al. 2013).

Conclusions

The nuclear receptor Rev-erbα acts in a tissue-specific manner to regulate circadian rhythms as well as metabolism, in some cases acting redundantly with Rev-erbβ. A critical question is whether Rev-erbα 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.

Acknowledgments I thank members of my research group, particularly Logan Everett, for helpful discussions. Research on Rev-erb in my laboratory is supported by NIH grant R01 DK45586 (MAL).

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