Targeting Nuclear Receptors for Th17-Mediated Inflammation: REV-ERBerations of Circadian Rhythm and Metabolism

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Abstract

Since their discovery, a significant amount of progress has been made understanding T helper 17 (Th17) cells’ roles in immune homeostasis and disease. Outside of classical cytokine signaling, environmental and cellular intrinsic factors, including metabolism, have proven to be critical for non-pathogenic vs pathogenic Th17 cell development, clearance of infections, and disease. The nuclear receptor RORγt has been identified as a key regulator of Th17-mediated inflammation. Nuclear receptors regulate a variety of physiological processes, ranging from reproduction to the circadian rhythm, immunity to metabolism. Outside of RORγt, the roles of other nuclear receptors in Th17-mediated immunity are not as well established. In this mini-review we describe recent studies that revealed a role for a different member of the nuclear receptor superfamily, REV-ERBa, in the regulation of Th17 cells and autoimmunity. We highlight similarities and differences between reports, potential roles beyond Th17-mediated cytokine regulation, unresolved questions in the field, as well as the translational potential of targeting REV-ERBa.

Keywords

Th17 cell; nuclear receptor; RORγt; REV-ERB; T regulatory; inflammation; metabolism

INTRODUCTION

IL-17-producing CD4+ T helper cells, Th17 cells, play critical roles maintaining immune system homeostasis at mucosal barriers, responding to extracellular pathogens to clear infection [1]. However, Th17 cells have garnered considerable attention given...
that dysregulated \( T_{H17} \) responses can contribute to autoimmune disease and chronic inflammation, including multiple sclerosis (MS) and psoriasis [2,3]. A number of \( T_{H17} \) cell types have been identified ranging from non-pathogenic \( T_{H17} \) cells (\( T_{H17n} \)) to pathogenic \( T_{H17} \) cells (\( T_{H17p} \)). \( T_{H17n} \) cells secrete IL-17 and IL-10 and work in an immune-modulating capacity in balance with forkhead box P3\( ^+ \) (Foxp3\( ^+ \)) T regulatory (Treg) cells. \( T_{H17p} \) cells secrete pro-inflammatory cytokines such as IL-17, interferon gamma (IFN\( \gamma \)), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [4–6]. Their non-pathogenic or pathogenic potential can be initiated by cytokines in the milieu at the time of naïve CD4\( ^+ \) T cell activation [7]. Alternatively, cellular metabolic processes, including glycolysis and oxidative phosphorylation (OXPHOS), play significant roles in the developmental potential of \( T_{H17} \) cells [8,9]. Specifically, increased aerobic glycolysis is strongly associated with \( T_{H17} \) cell pathogenicity, and while OXPHOS is also elevated in \( T_{H17p} \), inhibition of glycolysis appears to be more effective in preferentially targeting \( T_{H17p} \) vs \( T_{H17n} \) cells [8,9]. Finally, a coordinated network of transcription factors, including basic leucine zipper transcriptional factor ATF-like (BATF) and inter\( \alpha \)n-\( \alpha \)egulatory factor 4 (IRF4) initiate chromatin remodeling enabling other transcription factors, like signal transducer and activator of transcription 3 (STAT3) and RAR-related orphan receptor gt (ROR\( \gamma \), NR1F3), to influence nuanced \( T_{H17} \) cell development and effector functions [10,11]. STAT3 orchestrates expression of ROR\( \gamma \), the lineage defining transcription factor for \( T_{H17} \) cells, collectively modulating effector function through induction of key ROR\( \gamma /T_{H17} \) cell genes such I\( IL17a \) and I\( IL23r \)[10–12].

ROR\( \gamma \) is a member of the nuclear receptor (NR) superfamily of ligand regulated transcription factors. ROR\( \gamma \), however, is not the only NR associated with \( T_{H17} \) cell function. ROR\( \alpha \) (NR1F1), a close family member of ROR\( \gamma \), and REV-ERBa (NR1D1) have also been shown to be involved in the regulation of \( T_{H17} \) cell development and function [12–17]. REV-ERBa is encoded by the opposite DNA strand of the ERBA oncogene. Hence its name is derived from ‘reverse strand of ERBA’. NRs share a common core structure comprised of an amino terminus of variable length, a highly conserved central DNA binding domain (DBD), a lesser conserved ligand binding domain (LBD), and a flexible hinge region located between the DBD and LBD regions which often contains the nuclear localization sequence [18] (Figure 1A). Despite the high degree of sequence similarity of NRs, largely in their DBDs, they are functionally diverse through their differential recruitment of coregulators and subsequent chromatin remodelers. NRs interact with coregulators through both ligand-independent and dependent mechanisms. Specific coregulator interaction enables NR-target gene transcription. Binding of endogenous ROR\( \gamma \) agonist ligands such as oxysterols and other cholesterol metabolites can increase recruitment of coactivator steroid receptor coactivator-1 (SRC-1) increasing chromatin accessibility at ROR\( \gamma \) DNA recognition elements [19,20]. SRC-3 has been shown to be required for ROR\( \gamma \)-mediated \( T_{H17} \) cell pathogenicity [21]. Due to their pro-inflammatory role in several autoimmune and chronic inflammatory diseases, \( T_{H17} \) cells and ROR\( \gamma \) have been a pharmacological target for over a decade. ROR\( \gamma \)’s translational potential has been exploited by numerous pharmaceutical companies. To date, approximately 20 candidate compounds have entered clinical trials [22]. Unfortunately, most of the candidates were either discontinued or suspended for further development due to safety concerns or lack
of clinical efficacy [22]. Therefore, there is a need to understand these concerns and identify other potential therapeutic targets for the treatment of TH17-mediated inflammatory diseases.

REGULATION OF T_{H}17 CELLS BY THE NUCLEAR RECEPTORs REV-ERB{\alpha} and REV-ERB{\beta}

The REV-ERBs, REV-ERB{\alpha} and REV-ERB{\beta} (NR1D2), are two members of the NR superfamily and highly conserved proteins. Unlike most NRs, the REV-ERBs lack the conserved C-terminal helix necessary to recruit coactivator proteins and therefore interact exclusively with corepressors, including Nuclear Receptor Corepressor (NCoR). As a result, the REV-ERBs exclusively repress transcription. The REV-ERBs share a DNA response element, termed a RORE (ROR-response element), with the ROR NRs. Whereas the RORs activate, the REV-ERBs repress target gene transcription at these sites (Figure 1B). This opposing activity ensures temporal control of target gene expression in tissues where the REV-ERBs and RORs are co-expressed, including brain, liver, adipose tissue, and skeletal muscle [23]. This coordinated regulation of shared target genes by the RORs and REV-ERBs contributes to the circadian rhythm in mammals. The circadian rhythm is comprised of feedback loops of proteins that make up the molecular clock. Heterodimers of the transcription factors brain and muscle ARNT-like 1 (BMAL1) and circadian locomotor output cycles protein kaput (CLOCK), known as the positive limb of the circadian clock, induce the expression of the negative limb, cryptochrome (CRY1 and CRY2) and period (PER1, PER2, and PER3) circadian clock genes. As CRY and PER reach critical levels in the cell, they repress the expression of BMAL1/CLOCK heterodimers, thus downregulating their transcriptional activity. The RORs and REV-ERBs form an essential accessory loop resulting in further positive and negative regulation of gene transcription, respectively. Importantly, they co-regulate genes in the core circadian clock, including BMAL1. The expression of these proteins oscillates over the course of a 24 h period and regulate the expression of cell type-specific target genes to produce rhythmic expression [24]. These circadian processes have been well defined in several cell types including liver, skeletal muscle, and adipose tissue. While it remains unclear whether T cells undergo circadian regulation, some evidence suggests the REV-ERBs and RORs together with Nuclear Factor Interleukin 3 Regulated (NFIL3) exert circadian regulation of T_{H}17 cells [17,25,26].

Recent evidence from our lab and others have shown that the REV-ERBs and RORs are also co-expressed in T_{H}17 cells [14,16,17]. REV-ERB{\alpha} in particular exhibits T_{H}17 cell-specific expression relative to the other T helper subtypes. In line with REV-ERB{\alpha}’s role as a repressor, REV-ERB{\alpha}-deficient (Nrl1d1^−/−) T_{H}17 cells exhibit increased expression of core ROR{\gamma}T_{H}17 cell genes, including II17a, II17f, and II23r, when assessed by RNA-sequencing [14]. Reciprocally, overexpression of REV-ERB{\alpha} results in repression of these core target genes [14,16]. Mechanistically, ChIP-sequencing and ChIP-qPCR data show REV-ERB{\alpha} directly competes with ROR{\gamma} for binding at shared target sites within the regulatory elements of core T_{H}17 cell genes, including II17a and II23r [14,16]. Using in vivo models of T_{H}17 cell-mediated autoimmunity, including experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, global REV-
ERBα deficiency exacerbates disease severity by increasing CD4+ T cell number and pro-inflammatory cytokine expression in the central nervous system (CNS). It is important to note that increased disease scores in REV-ERBα deficient mice could be a consequence of general disruption of the circadian system, which is associated with higher inflammation levels [27]. Similar results to the EAE model were observed in colons of Rag1−/− mice, which are devoid of T and B cells, receiving Nr1d1−/− T cells in an adoptive transfer model of colitis [14]. In this model intraperitoneally delivered T cells are activated by gut microbes to elicit inflammation that models human colitis. In contrast, a separate study demonstrated T-cell specific loss of both REV-ERBα and REV-ERBβ leads to decreased T<sub>H</sub>17 cells and disease score in mice with EAE [16]. This data is consistent with work published several years earlier demonstrating a link between the circadian clock and T<sub>H</sub>17 cell development [17]. Intriguingly, induction of REV-ERBα expression in REV-ERBα-deficient T<sub>H</sub>17 cells delays EAE onset and limits disease progression [16]. Overall, these findings indicate REV-ERBα competes with RORs for binding at regulatory elements within core T<sub>H</sub>17 cell genes and differential expression of REV-ERBα can restrain T<sub>H</sub>17 cell pathogenicity.

Given the REV-ERBs are members of the NR family of ligand-regulated transcription factors, they are amenable to regulation by small molecule ligands [23,28–30]. Indeed, several synthetic ligands have been reported to modulate REV-ERB activity. SR9009 and SR12418 enhance REV-ERB-dependent target gene repression and have sufficient in vivo exposure to interrogate ligand-dependent activity in vivo [14,16]. Despite the conflicting genetic data, consistent with their expected role in enhancing REV-ERB-dependent repression, REV-ERB ligands limit disease progression in both chronic and relapsing-remitting models of EAE by inhibiting pro-inflammatory T<sub>H</sub>17 cell development, migration, and effector function in the CNS [14,16,17]. Although some studies have suggested REV-ERB-mediated target gene repression may be saturated due to their basal repressive activity or the presence of their endogenous ligand, these data using synthetic ligands indicate REV-ERB activity is not saturated in T<sub>H</sub>17 cells. Furthermore, mechanistic studies showed these ligands operate by enhancing corepressor recruitment at target sites including the Il17a locus [16]. Although these studies provide compelling evidence that REV-ERB ligands modulate T<sub>H</sub>17 cell activity, recent work has suggested that SR9009 has REV-ERB-independent effects on cellular metabolism. However, direct experimental evidence supports the conclusion that SR9009-dependent activity in T<sub>H</sub>17 cells is specific to REV-ERB modulation since ligand-dependent repression of IL-17A is lost in REV-ERBα/β double knockout (DKO) T<sub>H</sub>17 cells [16]. Our group has also successfully recapitulated these experiments (unpublished data); however, we acknowledge this is a single target gene and whether more global transcriptional changes are specific to ligand-mediated REV-ERB repression will need to be explored in greater detail. Going forward, it will be important to investigate whether newer generations of REV-ERB ligands with greater potency and specificity ameliorate disease in in vivo models of T<sub>H</sub>17-mediated autoimmunity [28,31]. Furthermore, it will be critical to include REV-ERBα/β DKO controls for all future experiments involving REV-ERB ligands.

Although published data defining a role for REV-ERBα in T<sub>H</sub>17 cells has been limited to mouse models, recent findings also support a role for REV-ERBα in human T<sub>H</sub>17 cells. REV-ERBα was identified as a T cell-specific MS susceptibility gene in a GWAS study.
from the MS Consortium, and REV-ERB\(\alpha\) was among the genes differentially expressed in \(T_{H17}\) cells derived from human patients [32,33]. Collectively, these findings indicate REV-ERB\(\alpha\) is a core regulator of \(T_{H17}\) cell-mediated autoimmunity in both mice and humans and therefore may be a viable target for small molecule therapeutics. This is important given that current therapeutics for autoimmune and chronic inflammatory diseases such as corticosteroids and aminosalicylates have negative side effects or variable efficacy [34–36]. Furthermore, results from the ROR\(\gamma t\) modulator clinical trials have been disappointing [22]. Thus, there is a need for more treatment options and targeting REV-ERB\(\alpha\) could be a new opportunity worth pursuing. However, since REV-ERBs are globally expressed and important for maintaining the circadian rhythm, it may be necessary to simultaneously pursue \(T_{H17}\) cell-specific targeted delivery of REV-ERB ligands (i.e., through antibody-drug conjugates) to avoid deleterious off-target effects [37]. It may also be important to consider the timing of therapeutic administration given the possibility that REV-ERB expression in \(T_{H17}\) cells could undergo circadian fluctuations.

Genetic and pharmacological studies indicate a role for REV-ERB\(\alpha\) as a repressor of \(T_{H17}\) cell pathogenicity; however, a role for its closely related sister protein REV-ERB\(\beta\) remains unclear. Intriguingly, while REV-ERB\(\alpha\) and REV-ERB\(\beta\) expression and activity has been shown to be redundant in most tissues, \(T_{H17}\) cells appear to be unique in that the two REV-ERBs exhibit differential expression and activity. Although overexpression of REV-ERB\(\beta\) largely phenocopies overexpression of REV-ERB\(\alpha\), it remains unclear how REV-ERB\(\beta\) deficiency affects \(T_{H17}\) cell activity. Current evidence includes \(T_{H17}\) cells deficient in both REV-ERBs (REV-ERB\(\alpha\)/\(\beta\) deficient), an EAE model using the \(T\) cell-specific REV-ERB\(\alpha\)/\(\beta\) DKO mice, and a mouse model of circadian disruption assessing intestinal \(T_{H17}\) cell frequencies [16,17]. REV-ERB\(\alpha\)/\(\beta\) DKO \(T_{H17}\) cells had the opposite phenotype of REV-ERB\(\alpha\) single deficient cells and REV-ERB\(\alpha\) deficient mice such that disease was ameliorated by loss of both REV-ERBs [16]. This contradicts the repressive effect of REV-ERB\(\alpha\) and REV-ERB\(\beta\) overexpression, as well as the repressive effect of REV-ERB ligands, which are expected to activate both REV-ERBs. One confounding variable that could underlie this discrepancy is the repression of REV-ERB\(\beta\) by REV-ERB\(\alpha\) such that REV-ERB\(\alpha\) knockout results in higher REV-ERB\(\beta\) expression. However, REV-ERB\(\alpha\) itself, as well as REV-ERB\(\beta\), have been demonstrated to negatively regulate REV-ERB\(\alpha\) [38,39]. Given this information, it is possible that loss of REV-ERB\(\beta\) leads to increased REV-ERB\(\alpha\) expression thereby presenting an alternative hypothesis for the data currently at hand. Thus, more comprehensive experiments are needed to define the unique role for REV-ERB\(\beta\) in \(T_{H17}\) cells.

Outside of the immune system, the REV-ERBs and RORs participate in regulating the circadian clock such that many of their tissue-specific target genes undergo rhythmic expression [23]. Much like the genetic data surrounding REV-ERB\(\alpha\) in \(T_{H17}\) cells, there is conflicting evidence as to whether adaptive immune responses, including \(T\) cell gene expression and effector responses, are affected by circadian rhythms [25,26,40]. Previous work showed that \(T_{H17}\) cells in particular are strongly influenced by the circadian clock. This seems logical given the lineage-defining transcription factor in \(T_{H17}\) cells, ROR\(\gamma t\), is an isoform of a core circadian protein (ROR\(\gamma\)). In hepatocytes, ROR\(\gamma\) is thought to be the dominant circadian factor driving rhythmic gene expression [41–43]. The study

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exploring a role for REV-ERBα in circadian T\textsubscript{H}17 cell activity found loss of REV-ERBα inhibits T\textsubscript{H}17 cell differentiation [17]. REV-ERBα worked in concert with another circadian protein, NFIL3 (also known as E4BP4), to control ROR\textsubscript{γt} expression and thus, T\textsubscript{H}17 cell development. The discrepancy between this finding and our published data could be due to differences in microbiota between the mouse facilities or the genetic background of the REV-ERBα-deficient mice, which were engineered differently. Regardless, both point to a critical role for REV-ERBα in regulating T\textsubscript{H}17 cell activity and a role for the circadian clock in adaptive immunity.

A large body of evidence indicates that metabolic genes are regulated by the circadian clock [44,45]. Indeed, REV-ERBα has been shown to orchestrate circadian control of metabolic genes in liver, adipose tissue, and skeletal muscle [23]. In the liver, changes in glucose availability affect the synthesis of the natural REV-ERB ligand, heme. Heme subsequently enhances REV-ERBα repression of metabolic genes, forming a negative feedback loop. Intriguingly, changes in metabolism are also a hallmark feature of T\textsubscript{H}17p vs T\textsubscript{H}17n cells. T\textsubscript{H}17p cells exhibit an overall increase in metabolism, particularly glycolysis, as well as changes in fatty acid composition [9,46–48]. Changes in fatty acid composition have been shown to influence ROR\textsubscript{γt} activity through modulation of the ROR\textsubscript{γt} ligand pool, which subsequently increases pathogenic gene expression [48]. Whether REV-ERBα is similarly regulated by changes in metabolism in T\textsubscript{H}17 cells (i.e., through modulation of heme or lipid synthesis) requires further investigation. At the same time, REV-ERBα activity has been shown to enhance oxidative phosphorylation and mitochondrial biogenesis in muscle tissue [49]. To our knowledge, the effect of REV-ERBα deficiency or ectopic overexpression on T\textsubscript{H}17 cell metabolism remains to be explored. For such studies, it will be important to compare effects in T\textsubscript{H}17n vs T\textsubscript{H}17p cells in vitro, as well as in vivo-derived cells due to the significant metabolic differences reported for in vitro vs in vivo T cells [50,51]. It will also be important to include REV-ERB ligands in these studies to determine whether effects can be ligand-regulated. These experiments exploring whether REV-ERBα contributes to the regulation of T\textsubscript{H}17 cell metabolism could uncover exciting new avenues in our understanding of T\textsubscript{H}17 cell activity.

**PERSPECTIVE**

T\textsubscript{H}17 cells are a central driver of several autoimmune and chronic inflammatory diseases, many of which are in need of safer and more effective treatment options. Thus, a better understanding of the factors that globally regulate the T\textsubscript{H}17 cell phenotype is paramount to developing new therapeutics. Recent evidence has shown pathogenic T\textsubscript{H}17 cells undergo metabolic remodeling to meet their increased demand for energy and biomolecular building blocks. This observation has led to the idea that T\textsubscript{H}17p cells can be specifically targeted with therapeutics aimed to inhibit these upregulated processes. At the same time, work from our lab and others have identified REV-ERBα as a critical regulator of T\textsubscript{H}17 cell pathogenicity. This experimental evidence from mouse models is supported by genetic evidence from human patients which also found REV-ERBα expression is associated with disease susceptibility. Excitingly, REV-ERBα is amenable to ligand regulation and small molecule ligands that enhance REV-ERBα activity ameliorate disease in several models of autoimmunity. Given that REV-ERBα has been shown to regulate metabolic processes...
in most tissues in which it is expressed (i.e., liver, adipose tissue, and skeletal muscle), it is not unlikely that REV-ERBα may also regulate T\textsubscript{H17} cell metabolic processes. Thus, we propose that efforts to better understand and target REV-ERBα-mediated regulation of T\textsubscript{H17} cell activity and metabolism would complement current campaigns to directly target T\textsubscript{H17p} cell metabolism. However, given the conflicting genetic evidence regarding the role of REV-ERBα in T\textsubscript{H17} cell activity, further studies are warranted to resolve these contradictions. Investigations into REV-ERBα regulation by its natural ligand, heme, in T\textsubscript{H17} cells could also uncover new pathways linking REV-ERBα activity and metabolism. Overall, the current evidence suggests REV-ERBα is a compelling regulatory factor in T\textsubscript{H17} cells, and deeper exploration of REV-ERBα activity could offer a better understanding of T\textsubscript{H17} cell biology as well as new therapeutic opportunities.

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**ABBREVIATIONS**

- **T\textsubscript{H17}**: T helper 17
- **T\textsubscript{H17n}**: non-pathogenic T\textsubscript{H17}
- **T\textsubscript{H17p}**: pathogenic T\textsubscript{H17}
- **NR**: nuclear receptors
- **DBD**: DNA-binding domain
- **LBD**: ligand-binding domain
- **MS**: multiple sclerosis
- **EAE**: experimental autoimmune encephalitis
- **Treg**: T regulatory cell
- **OXPHOS**: oxidative phosphorylation
- **ROR**: RAR-related orphan receptor
- **STAT**: signal transducer and activator of transcription
- **REV-ERBα**: reverse strand of ERBA
- **Foxp3**: forkhead box p3
- **NFIL3**: Nuclear Factor Interleukin 3 Regulated
- **BMAL1**: brain and muscle ARNT-like 1
- **CLOCK**: circadian locomotor output cycles protein kaput
PER1  Period 1
CRY1  Cryptochrome 1
NCoR  Nuclear Receptor Corepressor

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Figure 1. Nuclear receptor structure and function.

(A) The conserved nuclear receptor domain architecture from N- to C-terminus includes the activation function-1 (AF-1) domain, which is thought to perform ligand-independent activities. The AF-1 is followed by the DNA binding domain (DBD), which recognizes, and binds target sites on DNA. The hinge region provides a flexible linker between the DBD and the LBD, which binds ligands and coregulator proteins. The LBD includes the activation function-2 (AF-2) helix, which is critical for recruiting coactivator proteins.  

(B) Schematic depicting reciprocal regulation of shared target genes by RORs and REV-ERBs. RORs activate transcription at ROR response elements (ROREs) by recruiting coactivator proteins via their AF-2 helix. REV-ERBs compete for binding and repress transcription at these shared sites by recruiting corepressors (e.g., NCoR); since REV-ERBs lack the AF-2 helix, they cannot recruit coactivators or activate transcription.
Figure 2.
Proposed mechanism for ligand-dependent REV-ERBα activity in inhibiting metabolism in TH17p cells.