

REVIEW

NCOR1—a new player on the field of T cell development

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Abstract

Nuclear receptor corepressor 1 (NCOR1) is a transcriptional corepressor that links chromatin-modifying enzymes with gene-specific transcription factors. Although identified more than 20 years ago as a corepressor of nuclear receptors, the role of NCOR1 in T cells remained only poorly understood. However, recent studies indicate that the survival of developing thymocytes is regulated by NCOR1, revealing an essential role for NCOR1 in the T cell lineage. In this review, we will briefly summarize basic facts about NCOR1 structure and functions. We will further summarize studies demonstrating an essential role for NCOR1 in controlling positive and negative selection of thymocytes during T cell development. Finally, we will discuss similarities and differences between the phenotypes of mice with a T cell-specific deletion of NCOR1 or histone deacetylase 3 (HDAC3), because HDAC3 is the predominant member of the HDAC family that interacts with NCOR1 corepressor complexes. With this review we aim to introduce NCOR1 as a new player in the team of transcriptional coregulators that control T cell development and thus the generation of the peripheral T cell pool.

KEYWORDS

BIM, HDAC3, positive and negative selection, survival, T cells, thymocytes

1 | INTRODUCTION

T cell development is probably one of the best described developmental systems in mammals. T cells develop in the thymus and during their ontogeny several cell fate decisions are made and lineage-specific gene expression patterns are established and maintained.^{1,2} Similarly, peripheral T helper (Th) subsets have to establish distinct transcriptional programs to exert their characteristic effector functions upon antigen-specific activation by antigen-presenting cells. Within Th differentiation processes, lineage-defining transcriptional regulators instruct specific transcriptional programs. On top, epigenetic mechanisms such as post-translational modifications of histones that change the chromatin to either an “opened” or

“closed” state play crucial roles in the establishment and maintenance of Th-specific gene expression programs, although plasticity of Th subsets has been identified.^{3–7} Nuclear receptor corepressor 1 (NCOR1) is a transcriptional coregulator that bridges repressive chromatin-modifying enzymes such as histone deacetylases (HDACs), in particular HDAC3, with transcription factors. In this review, we will provide an overview about the role of NCOR1 in T cells. We will first briefly present basic facts about NCOR1, provide a short overview about T cell development, and then highlight recent genetic studies that indicate an important role for NCOR1 during T cell development. Finally, we will close the review by describing similarities and differences in the development of T cells in mice with a T cell-specific deletion of either NCOR1 or HDAC3.

Abbreviations: AP-1, activator protein 1; BAK, BCL-2 homologous antagonist/killer; BCL, B cell lymphoma; BCLXL, B cell lymphoma extra large; BIM, BCL-2 interacting mediator of cell death; BTB, bric-a-brac, tramtrack and broad complex; CD4SP, CD4 single positive; CD8SP, CD8 single positive; cKO, conditional knockout; DAD, deacetylase activation domain; DN, double negative; DP, double positive; EGR, early growth response; FASL, first apoptosis signal receptor ligand; FTOC, fetal thymic organ culture; HAT, histone acetyltransferase; HDAC, histone deacetylase; HID, histone interaction domain; IEL, intraepithelial lymphocyte; iNKT, invariant natural killer T cell; MAIT, Mucosal associated invariant T cells; MAZR, Myc-associated zinc finger-related factor; MeCP2, methyl-CpG-binding protein 2; MyoD, myogenic differentiation factor D; NCOR, nuclear receptor corepressor; NR, nuclear receptor; Pit-1, pituitary-specific positive transcription factor; PLC, phospholipase C; PLZF, promyelocytic leukemia zinc finger protein; RD, repression domain; RID, receptor interacting domain; ROR γ , RAR-related orphan receptor gamma; SEB, staphylococcal enterotoxin B; SMRT, silencing mediator for retinoid and thyroid hormone receptors; SP, single positive; TCR, T cell receptor; tg, transgene; Th, T helper; T_{reg}, regulatory T cell; WT, wild-type; ZF, zinc finger

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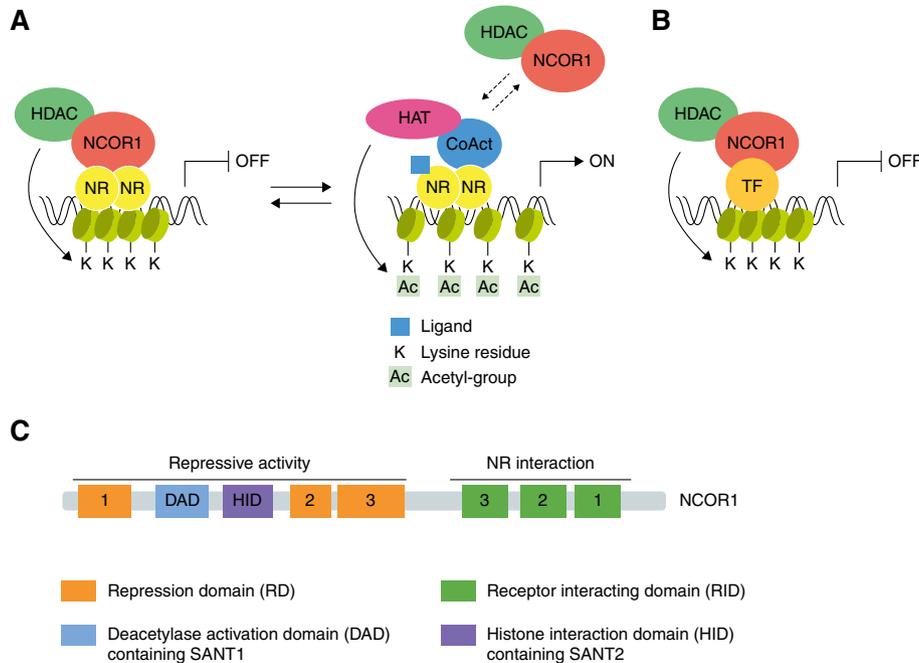


FIGURE 1 NCOR1-mediated gene regulation and NCOR1 structure and function. (A) NCOR1 mediates transcriptional repression by bridging histone deacetylases (HDACs), in particular HDAC3, with nuclear receptors (NR) in the absence of their ligands. Direct activation of NRs by ligand binding induces a conformational change followed by the exchange of NCOR1 corepressor complexes with coactivator complexes (CoAct). Coactivator complexes are usually associated with histone acetyltransferases (HATs), which promote transcription. For reasons of clarity of the drawing, other components of the corepressor or coactivator complexes and additional interacting factors/complexes have been omitted.⁹ Arrows from HDACs or HATs indicate deacetylation or acetylation of lysine residues on histone tails, respectively. (B) NCOR1 interacts also with other transcription factors (e.g. transcriptional repressors) and thus regulates their repressive activity. (C) Schematic drawing of the domain structure of NCOR1. The repressive function of NCOR1 is dependent on three repression domains (RD) located at the N-terminal part of NCOR1. RDs have been shown to actively recruit proteins of repressor complexes. Histone deacetylation is mediated by the deacetylase activation domain (DAD) and histone interaction domain (HID). These domains contain SANT-like motifs (named after their presence in Swi3, Ada2, NCOR1/SMRT and TFIIB), which promote the deacetylation of histones. Further, DAD is required for HDAC3 recruitment and HDAC3 enzymatic function. The C-terminal region of NCOR1 is composed of several nuclear receptor interacting domains (RIDs), which mediate recruitment and binding of NCOR1 to DNA-bound unliganded NR. For more details about the functions of the various NCOR1 domains we refer the reader to recent reviews.^{10,26} Figure 1 has been adapted from reference¹⁰

2 | BASIC FACTS ABOUT NCOR1

NCOR1 (encoded by the *Ncor1* gene) was initially isolated in complex with unliganded thyroid hormone (TR) and retinoic acid receptors (RAR).⁸ NCOR1 is essential for mediating the transcriptional repression by these nuclear receptors (NRs) in the absence of their ligands via its interaction with HDACs, in particular HDAC3, although interactions with other HDAC members have been shown. Moreover, NCOR1 is also a corepressor of other NRs such as the peroxisome proliferator-activated receptors, liver X receptor, and estrogen-related receptor α (for a detailed description of how NCOR1 regulates NR-mediated transcriptional repression we refer to other reviews^{9–11}). NCOR1 is part of larger multi-subunit complexes and not only associates with members of the NR transcription factor family but also with several other transcription factors including AP-1,¹² Pit-1,¹³ MyoD,¹⁴ MeCP2,¹⁵ c-MYC,¹⁶ CREB,¹⁷ and with several BTB-ZF transcription factors such as BCL6,^{18,19} PLZF,²⁰ Kaiso,²¹ and MAZR.²² This indicates that the activity of a broad spectrum of transcription factors depends on NCOR1 corepressor complexes (Fig. 1A and B).

NCOR1 is a large protein of approximately 2450 amino acids with a molecular weight of 270 kDa and is closely related (approx.

40% amino acid sequence identity) to the corepressor SMRT (also known as NCOR2).^{23–25} NCOR1 contains several functional domains that mediate its repressive activity and binding to NRs (Fig. 1C).^{10,26} The *Ncor1* gene locus encodes, due to alternative splicing, several NCOR1 protein isoforms that differ in the number of nuclear receptor interaction domains (RIDs), which in turn might alter the function and activity of the respective NCOR1 isoforms.^{27–29} Interestingly, NCOR1 protein isoforms can exert opposite functions, as revealed in adipocytes.²⁸ Moreover, the generation of various NCOR1 isoforms is regulated by hormonal and metabolic signaling, highlighting the importance of the nutritional environment in regulating NCOR1 activity.³⁰ In humans, NCOR1 expression displays a broad tissue distribution, including brain, gastrointestinal tract, endocrine tissues, and reproductive organs (www.proteinatlas.org).^{31,32} A search in the ImmGen database (www.immgen.org)³³ reveals that NCOR1 is also widely expressed in all immune cell lineages including T cells.^{22,34–36} NCOR1 is predominantly found in the nucleus; however, cytoplasmic localization of NCOR1 has been reported as well.^{37–41}

Despite the high homology to SMRT, NCOR1 has essential and nonredundant functions during embryonic development, because germline deletion of NCOR1 is embryonic lethal at E15.5, showing

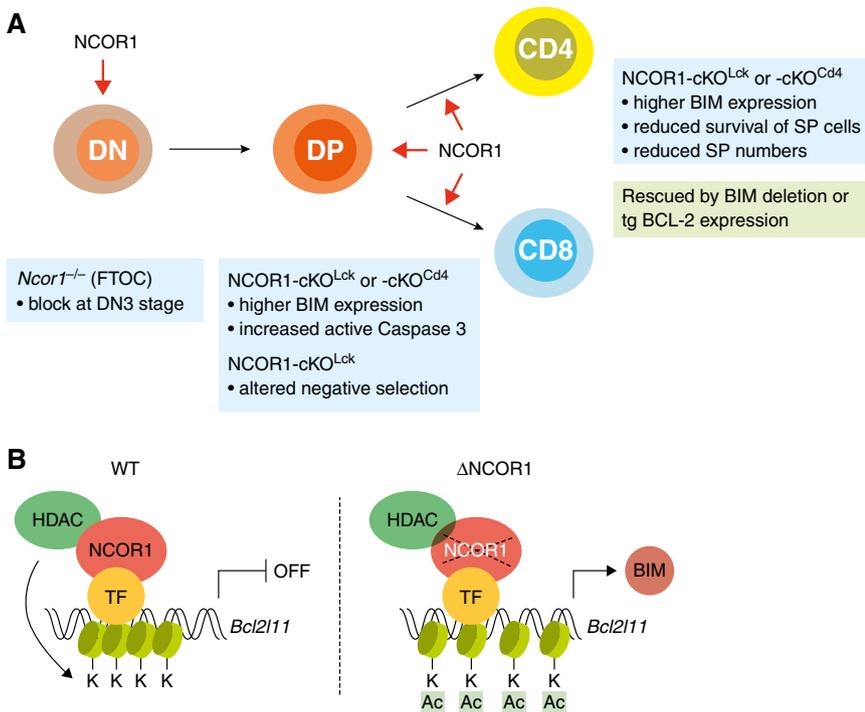


FIGURE 2 Schematic overview of NCOR1 functions during T cell development. (A) Simplified model of T cell development showing the four major thymocyte subsets based on CD4 and CD8 expression. Text boxes indicate the most prominent phenotypes observed in *Ncor1*^{-/-}, NCOR1-cKO^{Lck} and NCOR1-cKO^{Cd4} mice. (B) In DP thymocytes, NCOR1 is recruited to the *Bcl2/11* gene locus and represses the expression of BIM. The molecular identity of the transcription factor (TF) that recruits NCOR1 to the *Bcl2/11* locus is not known. Loss of NCOR1 leads to hyperacetylation of the *Bcl2/11* promoter and increased BIM expression. See text for more details

that SMRT is not able to compensate for the loss of NCOR1.⁴² Loss of NCOR1 affects many organs, tissues, and cell lineages. E13.5 *Ncor1*^{-/-} embryos show severe anemia and edema, which suggests altered erythropoiesis as the ultimate cause of death at E15.5.⁴² Additionally, NCOR1-deficient embryos have markedly reduced liver sizes and display a defect in CNS development between E12 and E15 as indicated by a size reduction of the developing thalamus.⁴² In order to overcome embryonic lethality of germline NCOR1-deficient mice and to study the function of NCOR1 in selected tissues and cell types, several laboratories generated mice that either harbor a conditional *Ncor1* deletion or express domain mutants of NCOR1. These studies (reviewed in^{10,11,43}) revealed important functions for NCOR1 in regulating skeletal muscle function and energy metabolism,^{44,45} hepatocyte biology,⁴⁶⁻⁴⁸ adipogenesis,⁴⁹ inflammation,⁵⁰ as well as intestinal epithelial cell maturation and homeostasis.⁵¹ Moreover, NCOR1 and SMRT are also linked to the pathogenesis of cancer and leukemia.²⁶

Reversible acetylation of lysine residues of histone proteins catalyzed by the opposing activities of histone acetyltransferases (HATs) and HDACs is one of the crucial mechanisms in epigenetic regulation of gene expression. In general, recruitment of HATs to the promoter regions of target genes leads to an open chromatin state and thus facilitates transcription, whereas recruitment of HDACs keeps the chromatin in a closed conformation and inhibits target gene transcription.⁵² HDAC3 was identified as the predominant catalytic component of NCOR1 and SMRT complexes and by interacting with gene-specific transcription factors NCOR1 recruits HDAC3 to promoter regions of NCOR1 target genes.^{10,53-55} Of note, HDAC3 requires binding to the DAD domain of either NCOR1 or SMRT for its enzymatic function,⁵⁵ indicating that NCOR1 regulates recruitment as well as the activity of HDAC3. The importance of NCOR1-HDAC3 interactions for the regulation of cellular function has been

reported in many biological processes including development,^{38,56} metabolism,⁵⁷⁻⁶⁰ and glucocorticoid receptor signaling.^{61,62} Apart from HDAC3, NCOR1 can also interact with class II HDACs (HDAC 4, 5, 7) as well as with HDAC1 in combination with the Sin3 repressor complex,⁶³⁻⁶⁵ thus broadening the spectrum of HDACs recruited to NCOR1 target genes. Additionally, NCOR1 mediates its repressive activity on target gene transcription by binding to some factors of the basal transcriptional machinery, thus preventing the formation of the transcription initiation complex.^{66,67}

3 | A BRIEF SUMMARY OF T CELL DEVELOPMENT

The two major subsets of conventional peripheral T cells, which express a TCR formed by the TCR- α and TCR- β chains, can be broadly divided into the MHC class II-restricted CD4⁺ Th cell lineage and the MHC class I-restricted CD8⁺ cytotoxic T cell lineage. Both T cell lineages develop in the thymus from a common progenitor in a fascinating biological process, which is also a great model system to study basic principles of cell fate decisions of progenitor cells to a particular lineage. Moreover, developing T cells are “educated” to distinguish between self and nonself, which is required for the establishment of immunologic tolerance. Based on the dynamic expression of the CD4 and CD8 coreceptor molecules one can define four major stages of T cell development (Fig. 2A). Impressive progress made during the last 20 years allowed the identification and characterization of several subpopulations within the four major developmental stages and revealed detailed molecular and cellular insight into the regulation of T cell development. In this review, T cell development will be only briefly discussed. For more details, we refer the readers to other

excellent reviews that provide a comprehensive discussion of major studies that shaped our current view on T cell development.^{1,2}

The earliest developmental stage in T cell differentiation is represented by double-negative (DN) thymocytes that do not express CD4 and CD8 coreceptors. DN cells can be further subdivided mainly by the expression of CD44 and CD25 into four consecutive differentiation stages (DN1-4). On DN3 cells, upon a productive recombination of the *Tcrb* chain, a pre-TCR is formed by a functional TCR- β and an invariant pre-T α chain. Signals through the pre-TCR lead to rapid proliferation and expansion of DN thymocytes (β -selection) and their progression to the CD4 and CD8 expressing double-positive (DP) stage. During the transition to the DP stage, re-expression of the *Rag* genes initiates the recombination of the *Tcra* locus and DP cells express a mature $\alpha\beta$ TCR formed by the TCR- α and - β chains. The newly paired $\alpha\beta$ TCR chains interact with self-peptides presented by MHC molecules and the resulting propagated TCR signaling strength decides on life or death of the DP cells. Here, pro- and anti-apoptotic members of the BCL-2 family such as BIM and BCL-2 are critical regulators of programmed cell death and thymocyte survival during positive and negative selection. The vast majority of DP cells express a TCR that fails to interact with self-peptide-MHC complexes on thymic epithelial cells and undergo death by neglect due to the lack of survival signals. DP or SP thymocytes with a strong TCR reactivity toward self-peptide-MHC complexes undergo apoptosis in a process termed negative selection. This negative selection process is mediated by the clonal deletion of thymocytes expressing high affinity/avidity TCRs and is required for the elimination of autoreactive T cells that might lead to autoimmune diseases. Finally, DP cells with low affinity/avidity TCR-self-peptide-MHC interaction receive survival signals and are positively selected. Moreover, at the onset of positive selection, CD4/CD8 cell fate decisions of DP thymocytes are initiated. DP cells expressing an MHC class-II-restricted TCR develop into CD4SP thymocytes composed of Th lineage cells including a minor fraction of FOXP3⁺ regulatory T cells, while DP cells expressing MHC-class I-restricted TCR develop into CD8SP thymocytes forming the cytotoxic T cell lineage. During the selection process, TCR-self-peptide-MHC signaling is supported by CD4 and CD8 through their function as coreceptors for MHC class II and MHC class I, respectively. For a detailed discussion of positive and negative selection as well as CD4/CD8 cell fate choice, we refer to several reviews that comprehensively summarize these topics^{1,2,68-72}. Collectively, these events result in the generation of CD4SP and CD8 SP thymocytes that, upon exiting the thymus, form the peripheral T cell pool with diverse specificities against a broad range of foreign antigens. In addition to conventional CD4⁺ Th cells and CD8⁺ cytotoxic T cells, also significant fractions of so-called unconventional T cells that are not selected on classical MHC molecules are generated during T cell development. These unconventional T cell subsets include iNKT cells, MAIT cells, IELs, and $\gamma\delta$ T cells and have, in contrast to conventional T cells, immediate effector function upon activation. Therefore, they are also termed innate-like T cells. These innate-like T cell subsets are very unique in their developmental and activation requirements, and we refer the interested reader to excellent reviews covering this highly complex topic.⁷³⁻⁷⁶

4 | NCOR1 AND THE REGULATION OF T CELL DEVELOPMENT AND T CELL FUNCTION

As discussed earlier, NCOR1 interacts with members of the BTB-ZF transcription factor family, which are key regulators of T cell development and function,^{77,78} suggesting that NCOR1 might also have important functions in T cells. Indeed, a very early study indicated already that NCOR1 is essential for proper T cell development. It has been shown that fetal E14.5 DN thymocytes isolated from *Ncor1*^{-/-} embryos are severely impaired in their progression to the DP stage after 3 days in in vitro fetal thymic organ cultures (FTOC). Of note, a large number of dead cells were observed in *Ncor1*^{-/-} FTOCs, suggesting impaired survival in the absence of NCOR1.⁴²

To further study the role of NCOR1 during T cell development, two laboratories recently generated mice with a T cell-specific deletion of NCOR1. Wang et al. used the *Lck*-Cre (NCOR1-cKO^{Lck}) as well as the *Cd4*-Cre (NCOR1-cKO^{Cd4}) strains to delete NCOR1,³⁵ whereas our laboratory used the *Cd4*-Cre deleter strain.³⁶ Both studies show that total thymocyte numbers are not significantly changed; however, the percentages as well as the numbers of SP thymocytes are reduced in NCOR1-cKO^{Cd4} and NCOR1-cKO^{Lck} mice. As a consequence, this also leads to reduced numbers of peripheral T cells. Further, the generation of BM chimeric mice indicated that the reduction in the SP cell population is due to a T cell-intrinsic defect.^{35,36} As described above, SP cells are generated from DP thymocytes in a process termed positive selection. Thymocytes can be examined by the combined analysis of the dynamic expression levels of TCR- β and the sequential expression of the activation marker CD69 that defines distinct stages of positive selection.⁷⁹⁻⁸¹ In the absence of NCOR1, the frequencies and cell numbers of positively selected (TCR β ⁺CD69⁺) as well as mature (TCR β ^{hi} CD69⁻) thymocytes are severely reduced, indicating that NCOR1 is required for an efficient positive selection and generation of SP thymocytes. This defect is also not rescued by the expression of a transgenic MHC class II-restricted ovalbumin-specific OT-II TCR, indicating that the impaired positive selection is not the result of defects in the recombination of TCR- α and TCR- β chains in the absence of NCOR1.³⁶ TCR signaling pathways are normal in NCOR1-deficient thymocytes as evidenced by similar phosphorylation kinetics of PLC- γ , ERK1/2, and p38 MAPK, as well as by comparable CD69 expression levels of WT and NCOR1-cKO^{Lck} thymocytes following TCR stimulation in vitro.³⁵ Further, NCOR1-deficient thymocytes up-regulate also the expression of EGR2, CD127, and BCL-2 during positive selection,³⁶ which are key molecules that mediate the survival of DP cells during the progression toward the SP stage.⁸² This also indicates that the reduction of NCOR1-cKO^{Cd4} SP cells is not due an impaired expression of these molecules. Rather, the expression of the pro-apoptotic protein BIM that antagonizes the pro-survival function of BCL-2 in DP and SP thymocytes is dramatically increased in NCOR1-cKO^{Cd4} and NCOR1-cKO^{Lck} mice. Further, in NCOR1-cKO^{Lck} mice, cleaved caspase 3-positive DP thymocytes are enhanced by 2-fold whereas there is no increase in the expression of the pro-apoptotic factors FASL, TRAIL, TNF- α , and BAK in activated or nonactivated DP thymocytes in vitro,³⁵

indicating a role for NCOR1 specifically in controlling BIM-dependent apoptosis. These findings also suggest that BIM-mediated thymocyte apoptosis as well as accelerated BIM-dependent negative selection contribute to the reduction of cells undergoing positive selection and increased cell death of SP thymocytes in the absence of NCOR1.^{35,36} Indeed, by using a RIP-OVA mouse model that mimics negative selection of thymocytes activated by endogenously expressed antigens, Wang et al. revealed an enhanced negative selection in NCOR1-cKO^{Lck} mice, most likely due to enhanced BIM expression levels.³⁵ In contrast, we showed that negative selection as determined by the SEB-mediated clonal deletion of V β 8⁺CD4SP cells was normal in NCOR1-cKO^{Cd4} mice.³⁶ Differences and limitations of the experimental models applied to study negative selection might provide an explanation for the conflicting results.

The study by Wang et al. provides also insight into the molecular mechanism leading to the up-regulation of BIM in the absence of NCOR1. RNA-seq experiments revealed that *Bcl2l11* (encoding BIM) was among the up-regulated genes in NCOR1-deficient thymocytes, especially in response to in vitro TCR activation. ChIP-qPCR experiments showed that in thymocytes NCOR1 is recruited to the *Bcl2l11* promoter region and thus it is very likely that NCOR1 directly represses BIM expression. TCR-triggering on thymocytes induces clearance of NCOR1 from the *Bcl2l11* promoter correlating with increased BIM expression upon activation. Further, the *Bcl2l11* promoter is hyperacetylated in the absence of NCOR1, indicating that NCOR1 inhibits BIM expression by promoting histone deacetylation (Fig. 2B).³⁵ Of note, deleting the pro-apoptotic factor BIM in NCOR1-cKO^{Lck} mice³⁵ or transgenic overexpression of the BIM neutralizing pro-survival factor BCL-2 in NCOR1-cKO^{Cd4} mice³⁶ restores both frequencies and cell numbers of SP thymocytes in the absence of NCOR1. This further supports a role for NCOR1 specifically in controlling BIM-mediated thymocyte apoptosis by balancing the expression of pro- and anti-apoptotic proteins. Taken together, these two studies indicate that NCOR1 controls BIM expression levels to inhibit negative selection and to promote the survival of SP thymocytes.

Of note, as discussed earlier, NCOR1-cKO^{Lck} mice have normal numbers of DP thymocytes, indicating an unaltered developmental transition from the DN to the DP stage. This is surprising, because germline deletion of NCOR1 impairs the DN to DP transition in E14.5 FTOCs.⁴² This suggests a different requirement for NCOR1 in embryonic versus adult T cell development, for example, due to the expression of compensatory factors, or that T cell-extrinsic effects might result in the block at the DN stage. Alternatively, *Lck*-Cre-mediated deletion, which is initiated at the DN2 stage,⁸³ might be too late in development to affect the DN to DP transition. Additional studies using Cre deleter strains that are active before the DN stage (such as *Vav*-iCre that deletes in hematopoietic precursor cells) are required to resolve this issue. Nevertheless, the large number of dead cells observed in *Ncor1*^{-/-} FTOCs⁴² suggests a role for NCOR1 also in the regulation of fetal thymocyte survival, similar to its function identified in adult thymocytes.

NCOR1 is also important for the generation of iNKT cells, because there are reduced percentages of CD1d-tetramer positive thymocytes in NCOR1-cKO^{Lck} mice.³⁵ Similarly, there is a reduction of FOXP3⁺

regulatory T (T_{reg}) cells in the absence of NCOR1.^{35,36} Interestingly, Wang et al. observed a small relative increase in the percentage of FOXP3⁺ T_{reg} cells within the peripheral CD4⁺ T cell population in NCOR1-cKO^{Lck} mice,³⁵ whereas we observed in NCOR1-cKO^{Cd4} mice a mild relative reduction of the percentage of FOXP3⁺ T cells within the CD4SP subset as well as the peripheral CD4⁺ T cell population.³⁶ The reason for the inconsistent results regarding the fractions of FOXP3⁺ T_{reg} cells remains currently unknown; however, a recent study revealed that NCOR1 together with HDAC3 is required for optimal suppressive activity of regulatory T (T_{reg}) cells.³⁴ Mice with a T_{reg} cell-specific deletion of HDAC3 develop lethal autoimmunity because their T_{reg} cells exhibit a severely impaired suppressive activity. It is known that the optimal enzymatic function of HDAC3 requires binding to the DAD domain present in NCOR1 and SMRT complexes⁵⁵; therefore, the contribution of NCOR1/SMRT-HDAC3 complexes in maintaining T_{reg} cell function was investigated. Indeed, the disruption of NCOR1/SMRT-HDAC3 interaction in mice expressing NCOR1/SMRT with mutated DAD variants led to the generation of FOXP3⁺ T_{reg} cells with a strongly impaired ability to inhibit T cell proliferation.³⁴ Together, these data indicated an important role for NCOR1 also in the development of T_{reg} cells and that the association of HDAC3 with NCOR1 (and/or the related factor SMRT) is crucial for an optimal suppressive activity of peripheral T_{reg} cells.

5 | T CELL DEVELOPMENT IN THE ABSENCE OF NCOR1 OR HDAC3—SIMILAR OR DIFFERENT PHENOTYPES?

As described earlier, NCOR1 controls the survival at distinct developmental stages. Because HDAC3 is the main HDAC member associated with NCOR1 corepressor complexes, one might expect that loss of HDAC3 in T cells leads to similar phenotypes. Indeed, several studies showed that HDAC3 is an important regulator of T cell development as well as of T_{reg} cell functions.^{34,84–88} Early deletion of HDAC3 in common lymphoid progenitor cells (CLPs) using the *Cd2*-iCre transgene (HDAC3-cKO^{iCd2}) or in DN thymocytes using the *Lck*-Cre deleter strain (HDAC3-cKO^{Lck}) leads to a developmental block at the DP stage due to a defect in positive selection,^{85,87} which is reminiscent of the developmental alterations observed in NCOR1-cKO^{Lck} and NCOR1-cKO^{Cd4} mice. This suggests synergistic functions for NCOR1 and HDAC3 during T cell development; however, the detailed analysis of conditional NCOR1 or HDAC3 knockout mice reveals clear differences in the requirement for NCOR1 and HDAC3 during T cell development, indicating nonoverlapping functions for both factors. One prerequisite for proper positive selection of DP cells is the down-regulation of ROR- γ t (encoded by the *Rorc* gene) upon TCR stimulation. ROR- γ t promotes the survival of DP thymocytes and its down-regulation allows the maturation to CD4SP and CD8SP thymocytes.⁸⁹ HDAC3-cKO^{iCd2} DP cells show increased histone acetylation at the *Rorc* promoter and fail to down-regulate ROR- γ t, leading to impaired positive selection.⁸⁷ Similarly, HDAC3-cKO^{Lck} DP thymocytes show increased *Rorc* mRNA expression.⁸⁵ NCOR1-cKO^{Cd4} and NCOR1-cKO^{Lck} mice also exhibit defects in positive selection^{35,36}; however, ROR- γ t

expression was properly down-regulated in signaled NCOR1-cKO^{Cd4} thymocytes during positive selection.³⁶ Further, positively selected NCOR1-cKO^{Cd4} SP thymocytes up-regulate EGR2 and express slightly elevated levels of CD127 and BCL-2,³⁶ whereas HDAC3-cKO^{iCd2} semi-mature TCR^β^{hi}CD24⁺ CD4SP thymocytes do not up-regulate CD127 and EGR2 and consequently do not induce BCL-2 expression.⁸⁷ In NCOR1-cKO^{Lck} and NCOR1-cKO^{Cd4} mice the defect in positive selection translates into reduced numbers of SP thymocytes compared to WT mice and as a consequence also in reduced peripheral T cell numbers. Strikingly, *Cd4*-Cre mediated targeting of HDAC3 during late T cell development (HDAC3-cKO^{Cd4}) does not alter the numbers or percentages of SP thymocytes, indicating a normal progression of positive selection.⁸⁶ Nevertheless, peripheral T cell numbers are severely reduced in HDAC3-cKO^{Cd4} mice. However, the majority of peripheral T cells are recent thymic emigrants due to a defect in post-thymic T cell maturation, as indicated also by the impaired up-regulation of the maturation marker CD55 in the absence of HDAC3.^{86,87} Similarly, peripheral T cell numbers are reduced in NCOR1-cKO^{Cd4} mice; however, CD55 expression levels are normal on peripheral NCOR1-cKO^{Cd4} T cells indicating that NCOR1, unlike HDAC3, is dispensable for post-thymic T cell maturation.³⁶

Although HDAC3 is the main HDAC family member associated with NCOR1 corepressor complexes, the comparison of NCOR1-deficient and HDAC3-deficient phenotypes suggests that NCOR1 and HDAC3 act in different pathways, and raises the question why the phenotypes observed upon deletion of NCOR1 and HDAC3 are quite distinct from each other. To explain the differences between the phenotypes, several possibilities are conceivable. First of all, different Cre deleter strains were used for targeting NCOR1 or HDAC3 during T cell development, potentially accounting for some of the differences observed. Moreover, we noted that NCOR1 protein is still detectable in NCOR1-cKO^{Cd4} DP thymocytes (despite an efficient genomic deletion of the floxed *Ncor1* alleles) and completely absent only from the SP thymocyte stage on.³⁶ In contrast, in HDAC3-cKO^{iCd2} mice no HDAC3 protein is detectable from the DN3 stage on.⁸⁷ Thus, residual NCOR1 protein present in NCOR1-cKO^{Cd4} DP thymocytes might recruit HDAC3 to some target genes and facilitates thereby, for example, the down-regulation of ROR-γt expression prior to positive selection. Further, it is also conceivable that the NCOR1-related factor SMRT takes over some of the functions and thus might compensate for the loss of NCOR1. Finally, although HDAC3 is an integral part of NCOR1 corepressor complexes,^{9,10} transcriptional regulation mediated by NCOR1 corepressor complexes might be not exclusively dependent on HDAC3 interactions. The observation that NCOR1 promotes deacetylation of the *Bcl2l11* promoter region to restrain BIM expression,³⁵ whereas BIM expression remains unaffected in the absence of HDAC3,⁸⁷ suggests the involvement of other HDAC family members. Additional studies that compare T cell development in mice where the same Cre deleter strain is used to delete NCOR1 or HDAC3 are required to resolve these issues. These studies should also include a careful examination of residual NCOR1 and HDAC3 protein levels in various subsets upon deletion of the *Ncor1* and *Hdac3* alleles as well as RNA-seq and ChIP-seq approaches to dissect NCOR1- and HDAC3-dependent transcriptional networks during T cell development.

6 | CONCLUDING REMARKS

Although NCOR1 was identified more than 20 years ago, and despite the characterization of many developmental and cellular processes regulated by NCOR1, there is still room to discover novel and important functions for NCOR1 and NCOR1-mediated processes. As briefly summarized in this review, NCOR1 is a crucial regulator of T cell development by controlling DP and SP thymocyte survival. Thus, the recently published studies on the role of NCOR1 in T cells added a previously unknown function for NCOR1, that is, the regulation of cell survival and apoptosis, to the growing list of biological processes that are controlled by NCOR1 in a cell type-specific manner. It would not be surprising if it turns out that NCOR1, which is a new player on the field of T cell development, has also other important roles throughout a T cell's life.

AUTHORSHIP

L.M., D.H., V.S., and W.E. wrote the review and made figures.

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DISCLOSURES

The authors declare no conflicts of interest.

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