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Review Article

Nuclear receptor corepressor complexes in cancer: mechanism, function and regulation

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Abstract: Nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT) function as corepressors for diverse transcription factors including nuclear receptors such as estrogen receptors and androgen receptors. Deregulated functions of NCoR and SMRT have been observed in many types of cancers and leukemias. NCoR and SMRT directly bind to transcription factors and nucleate the formation of stable complexes that include histone deacetylase 3, transducin β-like protein 1/TBL1-related protein 1, and G-protein pathway suppressor 2. These NCoR/SMRT-interacting proteins also show deregulated functions in cancers. In this review, we summarize the literature on the mechanism, regulation, and function of the core components of NCoR/SMRT complexes in the context of their involvement in cancers and leukemias. While the current studies support the view that the corepressors are promising targets for cancer treatment, elucidation of the mechanisms of corepressors involved in individual types of cancers is likely required for effective therapy.

Keywords: NCoR, SMRT, HDAC3, TBL1, TBLR1, GPS2, cancer, corepressor, transcriptional repression

Introduction: discovery of NCoR and SMRT as promiscuous nuclear receptor corepressors

The 'on'-and-'off' control of gene expression involves a cascade of transcription factors and is assisted by two classes of cofactors. These cofactors can activate (the coactivators) or repress (the corepressors) gene transcription via modifying specific residues of histones, thereby regulating the accessibility of chromatin to the basal transcription machinery [1]. Two of the first identified corepressors are nuclear receptor corepressors (CoRs), which include NCoR (nuclear receptor corepressor) [2] and SMRT (silencing mediator for retinoid and thyroid hormone receptors) [3]. Prior to the cloning of NCoR and SMRT, several studies have reported that thyroid hormone receptors (TR) and retinoic acid receptors (RAR) have an intrinsic ability to mediate ligand-independent repression, in a manner that is dependent on soluble and titratable factors [4-6]. The search for these factors led to the cloning of NCoR [2] and its homologous protein SMRT [3] (a truncated version) as well as full-length SMRT [7, 8]. Binding of TR and RAR to their respective ligands, thyroid hormone (T3) and retinoic acid (RA), disrupts their interactions with NCoR or SMRT, allowing for coactivator recruitment and subsequent activation.

Subsequent studies reveal that NCoR and SMRT also mediate ligand-independent interaction with various other nuclear receptors (NRs), including vitamin D receptors (VDR) [9], peroxisome proliferator-activated receptors (PPAR) [10], liver X receptors (LXR) [11], and with orphan receptors including Rev-Erb [12, 13], chicken ovalbumin upstream promoter transcription factor (COUP-TF) [14], and dose-sensitive sex reversal-AHC critical region on the X chromosome, gene 1 (DAX-1) [15]. NCoR and SMRT also have the ability to interact with steroid hormone receptors, namely, estrogen receptor (ER) [16], androgen receptor (AR) [17, 18], and progesterone receptor (PR) [19]. Although these interactions are generally weaker than the interactions with non-steroid receptors, the steroid receptor interactions with NCoR/SMRT can, nevertheless, be stabilized by

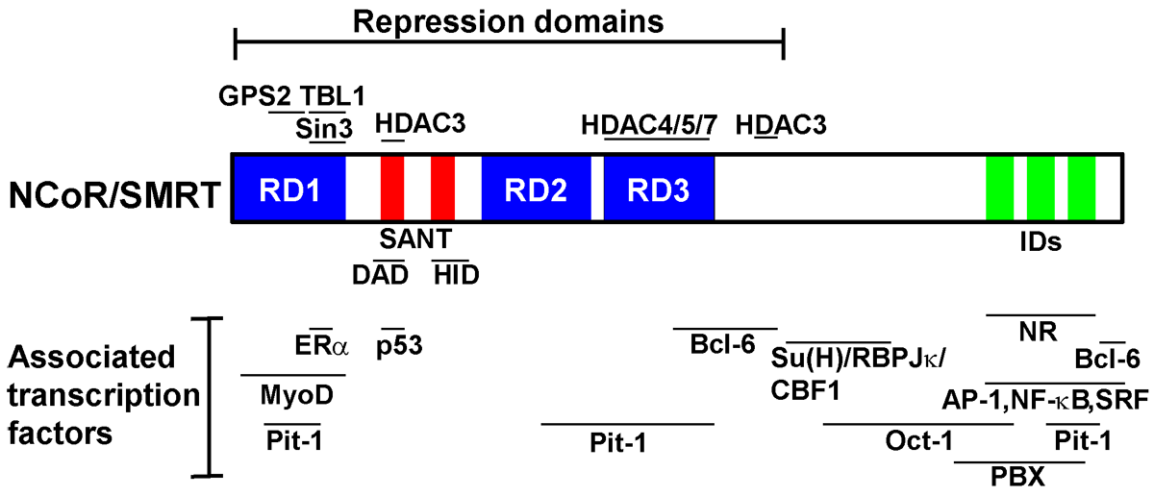

Figure 1. Diagram of NCoR/SMRT corepressors showing their regions involved in various interactions with nuclear receptors, other transcription factors as well as interactions with other components of the core complex.

binding to the corresponding antagonists. One of the best-studied examples is tamoxifen, an ERα antagonist used to treat ERα-positive breast cancers. Tamoxifen binding to ERα stabilizes the interaction between ERα and NCoR, which is considered a contributing factor for tamoxifen inhibition of ERα target gene expression [20].

Mechanism of action of NCoR/SMRT

NCoR and SMRT are 270 kDa proteins that share highly homologous domains. The C-terminal region of NCoR and SMRT contains three (NCoR) or two (SMRT) nuclear receptor interaction domains (IDs) that mediate direct interactions with the ligand-binding domain (LBD) of NRs [2] (**Figure 1**). The functional motifs of IDs contain the so-called CoRNR boxes, which have the consensus sequence L-X-X-I/H-I-X-X-X-L/I (L: leucine, I: isoleucine, X: any amino acids) [21-25]. The binding affinity is predominantly regulated by the conformational change of NR LBD domains that takes place in response to ligands (agonists or antagonists). Binding of agonists or antagonists to NRs induces the movement of the helix 12 region of NRs whose position dictates the binding ability of NCoR/SMRT. In general, agonists destabilize the corepressor interaction, resulting in the dismissal of CoRs and subsequent recruitment of coactivators to drive agonist-dependent transcriptional activation. Antagonists do the opposite by stabilizing NCoR/SMRT interactions. In addition, the specificity and fine tuning of the binding between NRs and N-CoR/SMRT are also shown by the preferential use of different CoRNR boxes within a single CoR molecule and the preferential use of NCoR or SMRT for the binding [26, 27].

Biochemical purification of NCoR and SMRT has shown that both NCoR and SMRT are present in large protein complexes (1.6-2 MDa size) that also contain histone deacetylase 3 (HDAC3), transducin β-like protein 1 (TBL1)/TBL1-related protein 1 (TBLR1), and G-protein pathway suppressor 2 (GPS2) [28-30]. It is likely that the core complex contains four subunits, two of which can be either NCoR or SMRT, and either TBL1 or TBLR1. A recent work has shown that TBL1 may exist as a tetramer [31]. The molecular weight of the core complex is about 412 KDa. Multiplication of this by 4 gives rise to~1.6 MDa, which is in the range of the observed size (1.6-2 MDa). Clearly, the NCoR/SMRT complex should also contain other sub-stoichiometric components, such as Sin3A/HDAC1 [32-37], Class II HDACs [38, 39], the subunits of chromatin-remodeling complexes [40], KAP-1 [40], and histone acetyl-transferases such as CBP [1, 41-43]. The functional interactions of these sub-stoichiometric components with the core NCoR/SMRT complex may offer additional layers of regulation of target gene transcription.

NCoR/SMRT nucleates the formation of the core complex through interactions provided by the N-terminal portion of the proteins.

Historically, the N-terminus of NCoR and SMRT has been characterized to contain three independent repression domains (RD1, RD2 and RD3) [2]. While the function of RD2 and RD3 has yet to be clarified, RD1 has been shown to mediate NCoR/SMRT interactions with both GPS2 and TBL1/TBLR1 [28, 44]. Interestingly, the region of RD1 that interacts with TBL1/TBLR1 appears to overlap with the recently-reported interaction with the DNA-binding domain of ERα [45] (**Figure 1**).

None of the three RD domains interacts with HDAC3. A previously-noted motif in NCoR and SMRT is the SW13/ADA2/NCoR/TFIIB (SANT) domain, two copies of which are located between RD1 and RD2 [46]. The first SANT domain along with a short upstream region is referred to as the deacetylase activation domain (DAD), which directly binds to HDAC3. The binding involves a conformational change of DAD and is critical for the activation of the enzymatic activity of HDAC3 [28, 47, 48]. Interestingly, a recent work [49] by Adikesavan et al. has shown that the DAD of SMRT can directly bind to p53 (**Figure 1**). This binding blocks HDAC3 interaction with DAD leading to a net increase in histone acetyltransferase (HAT) activities, which contributes to the activation of p53 target gene in response to DNA damage. SMRT (but not NCoR) has also been shown to function as a coactivator for ERα in MCF-7 breast cancer cells [50], underscoring a specificity between SMRT and NCoR in regulating transcription.

The second SANT domain in CoRs has been shown to function as a histone interaction domain (HID), in line with the reported role of SANT domains in recognizing histones in the context of other proteins [51]. By occupying the nonacetylated histone tails, HID inhibits HAT activities, suggesting a feed-forward mechanism by which the two SANT motifs cooperatively promote histone deacetylation and repression of target genes [52, 53]. Similar modes of cooperation have also been reported between HDAC3 and TBL1, which can also directly bind to histones [30, 54, 55].

Although NCoR and SMRT were originally identified as transcriptional corepressors for NRs, they have emerged as promiscuous corepressors for many other sequence-specific transcription factors that function in different cellular processes [42]. Thus, various studies have shown that SMRT and NCoR interact with Bcl-6/LAZ3, a transcription factor recently shown to play an important role in repressing inflammation [56-59], MyoD [60], HES-related repressor proteins [61]. NCoR/SMRT also interact with the evolutionarily related POU homeodomain factors Pit-1 [62, 63], Oct-1 [64], the Notch-activated adapter protein Su(H)/RBP-Jκ/CBF1 [65-67], Pbx [68, 69], serum response factor (SRF) [70], NF-κB [71-74], AP-1 [70], and signal transducers and activators of transcription 5 (STAT5). Other factors that are associated with NCoR and SMRT include PLZF [75, 76], ETO family proteins involved in acute myeloid leukemias [77-79], SMADs [80], c-Myb [81], aryl hydrocarbon receptor [82], Sharp [83], and Kaiso [84].

Two studies have added new insight into the function and mechanism of CoR-mediated repression. Ebert et al. showed that NCoR can interact with methyl-CpG-binding protein 2 (MeCP2) and phosphorylation of T308 blocks the interaction of the MeCP2 repression domain with NCoR and suppresses the ability of MeCP2 to repress transcription [85], thus linking NCoR to DNA methylation-dependent gene silencing. Another work shows that the NCoR complex binds and deacetylases P-TEFb, an elongation factor important for RNA Pol II-mediated transcription [86], thus revealing a role for corepressors in deacetylating general transcription factors to regulate transcription.

Deregulation of NCoR/SMRT corepressors and other complex subunits in cancer

ER and AR are steroid receptors that play important roles in the initiation and progression of breast and prostate cancers. NCoR/SMRT interact with both ER and AR and serve as potential drug targets in the treatment of these cancers. Recent genome-wide studies have shown that NCoR/SMRT and HDAC3 bind to thousands of genes [56, 87], consistent with their use by other transcription factors such as c-Jun and NFκB that impact on fundamental cellular activities. In this section, we summarize the literature on the involvement of NCoR/SMRT and other complex subunits in cancers and leukemias. NCoR and SMRT have been largely studied in the context of ER, AR and leukemia fusion proteins. While previous studies have focused on NCoR, SMRT and HDAC3, some new development has been reported for

TBL1/TBLR1 and GPS2, suggesting their important roles in cancer development.

NCoR and SMRT subunits

Breast cancer: ERα is expressed in approximately 75% of breast cancers where ERα - dependent activation plays an important role in the growth of these cancers. NCoR/SMRT are among the best-characterized ERα corepressors [88]. Since coactivators and corepressors compete for ERα binding, the ratio between coactivators and corepressors is expected to modulate ERα activity in benign and malignant cells. Results from independent studies have supported this model by showing that diminished expression of NCoR/SMRT drives breast cancer initiation and progression. For example, an unbiased pathway analysis has revealed multiple alterations linked to loss of NCoR and SMRT corepressor complexes in luminal A breast tumors [89]. In another study that examines ERα corepressor levels in breast cancer, NCoR levels were found to be downregulated in invasive ductal carcinomas [90].

Downregulation of NCoR/SMRT has also been implicated in endocrine resistance. Selective ER modulators (SERMs), such as tamoxifen, an ERα antagonist, are beneficial in the initial treatment of ERα-positive breast cancer, because these SERMs can inhibit cancer growth by inhibiting the transcriptional activity of ERα. The activity of tamoxifen is in part attributed to its ability to stabilize the binding of ERα to corepressors [91]. Reduced expression of NCoR/SMRT corepressors has been shown to contribute to tamoxifen resistance in breast cancers [92-95]. Two studies have provided mechanistic insights into signal-dependent downregulation of NCoR and SMRT in breast cancer cells at the level of protein degradation, which contributes to cancer progression and acquisition of endocrine resistance. Frasor et al. reported that NCoR level was reduced due to estrogen-dependent upregulation of Siah2, which functions as an E3 ligase for NCoR [96, 97]. Interestingly, two recent studies have shown that downregulation of Siah2 is correlated with acquisition of breast cancer tamoxifen resistance [98, 99]. In another work, Stanya et al. reported that Pin1 can promote proteasomal degradation of phosphorylated SMRT in response to HER-2 signaling [100].

Several studies have reported alternative mechanisms by which NCoR regulates ERα-dependent transcription in breast cancers. First, NCoR has been shown to regulate ERα expression. More than half of the ERα-positive breast cancers also express PR. Elevated expression levels of PR-B isoform increase the interaction of the receptor with NCoR on the half-PRE site of the ERα promoter, an event incompatible with PR-coactivator interactions. Silencing of NCoR was able to reverse the down-regulation of ERα expression induced by PR-B overexpression [101]. In another work, by using chromatin immunoprecipitation (ChIP) assays, Konduri et al. [102] have demonstrated that ERα represses p53-mediated transcriptional activation in human breast cancer cells by recruiting NCoR/SMRT and HDAC1. Finally, reduction in the ratio of ERβ to ERα expression appears to be correlated with breast tumorigenesis. Bartella et al. [103] showed that ERβ recruits NCoR, leading to hypoacetylation of histones and displacement of RNA-polymerase II at the ERα promoter, providing new mechanistic insight into the antagonism between ERβ and ERα in breast cancer cell growth.

Prostate cancer: AR is the driving force for prostate cancer development and progression. Many patients will benefit from the androgen deprivation therapy in combination with the treatment of AR antagonists (flutamide or bicalutamide). The underlying principle for the use of AR antagonists is that these compounds will compete with agonists for binding to AR, while stabilizing the binding between AR and NCoR/SMRT corepressors, thus preventing coactivator recruitment and AR-dependent activation of target genes [104, 105].

The involvement of AR corepressors in prostate cancer has been well documented [106]. Earlier studies have suggested that a reduction of NCoR/SMRT levels may contribute to androgen-independent AR activation and prostate cancer progression [107-109]. Nevertheless, several studies have shown that the corepressor regulation of AR may be more complex than previously thought. It has been shown that overexpression of NCoR/SMRT does not repress AR-dependent gene expression in prostate cancer cell lines, but rather activates it [110]. A caveat is that overexpressed proteins may not faithfully recapitulate the regulation observed under physiological conditions. Another work has shown that the ability of

NCoR to enhance antagonist-mediated AR repression is in fact modulated by post-translational modifications of NCoR. Protein kinase A (PKA) is able to directly bind and phosphorylate the Ser-70 residue in the RD1 domain of NCoR. The phosphorylation enhances nuclear localization of NCoR and potentiates the antagonist activity on AR-dependent transcription in prostate cells [111].

Several recent studies have re-affirmed the importance of AR-NCoR/SMRT axis in regulating AR function and prostate cancer progression. It has been shown that reduced recruitment and loss of corepressor SMRT/NCoR alter the ligand response and AR functions in a manner that contributes to prostate cancer progression [112]. In another study, Yoo et al. studied the role of AR corepressors during androgen-independent prostate cancer progression [113]. It was found that casein kinase 2 (CK2)-mediated phosphorylation of NCoR strongly correlates with androgen-independent growth and invasion of prostate cancer cells, and with poor prognosis of prostate cancer patients, suggesting that CK2-NCoR axis is a potential therapeutic target in prostate cancer. Perhaps a more exciting evidence for a direct role of NCoR in antagonizing androgen-independent prostate cancer growth is provided by the study showing that the ubiquitin ligase Siah2 switches AR from repressed to the activated state by selectively targeting NCoR bound, transcriptionally-inactive AR for ubiquitin-dependent degradation. Thus, Siah2 promotes activation of AR target genes, leading to the growth of androgen-independent prostate cancer cells [114]. Taken together, the consensus of the current studies is in line with the model that the efficacy of NCoR/SMRT corepressors in repressing AR activity is directly correlated with the recruitment of these corepressors on AR target genes. Reduction of such recruitment, which would predispose genes for activation, may occur through various mechanisms, such as reduced gene expression, proteasomal degradation or altered modification of the corepressors.

Leukemia: Leukemia is a prototypic type of cancer in which a pro-oncogenic function of NCoR and SMRT was first documented. One form of acute promyelocytic leukemia (APL) is caused by abbrant expression of PML-RARα (promyelocytic leukemia-retinoic acid receptor α) or PLZF-RARα (promyelocytic leukemia zinc finger-retinoic acid receptor α) fusion proteins. As a result of the fusion, the binding affinity between RARα and NCoR/SMRT is increased such that the corepressors cannot be released by the physiological dose of RA [75, 115-118]. Accordingly, these fusion proteins promote leukemogenesis due to reduced sensitivity to retinoic acid-dependent transcriptional activation of target genes involved in cell differentiation. The involvement of NCoR/HDAC in the pathogenesis of leukemias is further confirmed by the studies showing that expression of an NCoR fragment that disrupts corepressor interaction restores RA sensitivity in resistant cells [119], and that the NCoR/HDAC complex is a key regulator of the transcriptional repression mediated by PML-RARα in vivo [120]. APL patients that have PML-RARα is sensitive to high doses of RA treatment, whereas APL patients harboring PLZF-RARα translocations do not. This difference is due to the fact that in PLZF-RARα, the PLZF moiety can also bind to NCoR/SMRT corepressors, which cannot be released by high doses of RA, thus explaining the phenotypic difference between PML-RARα and PLZF-RARα. The presence of trichostatin A, a specific inhibitor of histone deacetylases, increases histone acetylation and leads to transcription activation [115].

Two recent studies have provided new insight into the regulation of RARα fusion proteins by NCoR/SMRT. One study shows that PML-RARα and PLZF-RARα have gained the ability to recognize specific spliced variants of NCoR and SMRT variants that are poorly recognized by RARα [121]. Another work showed that failure to dissociate corepressors, or failure to recruit co-activators results in RA-resistant variants of the PML-RARα oncoprotein in APL [122].

The t(8;21) chromosomal translocation is involved in nearly 15% of total acute myeloid leukemia (AML) cases, which generates the AML1-ETO fusion protein between the DNA-binding domain of AML1 and a nearly full-length ETO. The role of NCoR/SMRT corepressors in AML was first revealed by their interaction with ETO, the fusion partner in the t(8;21) AML and NCoR/SMRT [77, 123, 124]. ETO is a member of a small family of corepressors that can form oligomers and bind to NCoR/SMRT and HDACs [125, 126]. Its homologous protein ETO-2 is also involved in AML by fusing to AML1 [127]. The current literature is consistent with the model that the AML1-ETO/ETO-2 promote leu-

kemogenesis in part by recruiting the NCoR/SMRT/HDAC to repress transcription of target genes [77, 128-130]. Interestingly, a recent work has shown that another leukemia fusion protein E2A-Pbx1 drives leukemogenesis by escaping ETO-2-mediated repression in order to activate Hox target genes [131]. Thus, the role of corepressors in different types of leukemias is likely context-dependent, emphasizing the need to dissect the individual mechanisms for therapeutic targeting of the corepressors.

Other subunits of the NCoR/SMRT complex

HDAC3: HDACs deacetylate both histones and proteins, and play important roles in the regulation of chromatin biology and gene transcription [77, 132-134]. The 18 human HDACs can be divided into 4 classes [28]. Class I, II and IV belong to Zinc-dependent, NAD-independent histone deacetylases, whereas class III belongs to NAD-dependent histone deacetylases. Class I HDACs include HDAC1, 2, 3 and 8 isoforms, which are encoded by separate genes. The Class I HDACs generally show ubiquitous expression, and HDAC1-3 have been well studied. HDAC1 and HDAC2 exist as a dimer in several HDAC1/2-shared complexes, including the NURD chromatin-remodeling complex [135, 136], the Sin3A-containing corepressor complex and the CoREST/LSD1-containing histone deacetylase/histone demethylase complex [137, 138]. Whereas HDAC1 and HDAC2 generally show constitutive nuclear localization, HDAC3 shows both cytosolic and nuclear localization [139]. Consistent with this, HDAC3 contains both nuclear import and export domains [140]. In the nucleus, HDAC3 specifically associates with NCoR/SMRT corepressor complexes [28].

Several studies have implicated a role for HDAC3 in cancer. Upregulation of HDAC3 has been observed in several types of cancers including colon, lung, prostate and breast cancers, in a manner that correlates with poor survival and prognosis of the patients [141-148]. HDAC3 has served as a potential drug target in the treatment of PML-RARα, PLZF-RARα and AML1-ETO leukemias [77, 126, 149, 150]. Independent studies using cancer and leukemia-derived cell lines have confirmed pro-survival roles for HDAC3. The pro-survival activity of HDAC3 revealed by these studies may be mediated by its roles in transcriptional repression of growth-arrest genes such as p21 [55, 151, 152], cell cycle progression [153-155], genomic stability [156], or its involvement in apoptosis/cell death/survival pathways [141, 142, 150, 157-159]. In addition to regulating cell proliferation, HDAC3 has also been shown to play an important role in metastasis of cancer cells through its ability to enhance epithelial-mesenchymal transition (EMT) [160]. HIF-1alpha-induced HDAC3 was found to be crucial for hypoxia-induced EMT and metastatic phenotypes. HDAC3 crosstalks with WDR5 to activate the expression of mesenchymal genes expression, while repressing epithelial gene expression. While these studies have supported an anti-tumorigenic function of HDAC3, Bhaskara et al. have shown that mice depleted of HDAC3 in liver develop hepatocellular carcinoma [156, 161], suggesting that HDAC3 may have context-dependent function in different cancers.

An active area in HDAC study is the development of isoform-specific HDAC inhibitors [162-164]. While pan-HDAC inhibitors have promising effects in the treatment of cancers, the clinical use of these inhibitors is complicated by their off-target effects [165-168]. It has been proposed that HDAC3 may be responsible for most of the anti-tumor effects of HDAC inhibitors [154, 169]. A few studies reported the development and use of HDAC3-specific inhibitors that target the active form of HDAC3 [169, 170]. Inhibition of HDAC3 using such a selective inhibitor RGFP966 promotes apoptosis and diminishes cell growth in cutaneous T cell lymphoma cell lines due to DNA damage and compromised S phase progression [169].

An alternative strategy to inhibit HDAC3 function is to prevent its activation by blocking the formation of HDAC3 complexes with corepressors, based on findings that the enzymatic activity of HDAC3 is strictly dependent on its binding to NCoR/SMRT [28, 171]. The critical importance of corepressor interaction for HDAC3 activity has been recently demonstrated in vivo [172], which shows that mice harboring loss-of-function mutations in the DAD domain of both NCoR and SMRT have essentially no active HDAC3 in all tested tissues, which correlates with globally-increased histone acetylation. These mice, unlike the embryonic lethality of the total HDAC3 knockout mice [173], are vital, suggesting that free HDAC3 is not non-functional. A follow-up study by the Lazar group [174] recently showed that an HDAC3 mutant that is enzymatically inactive

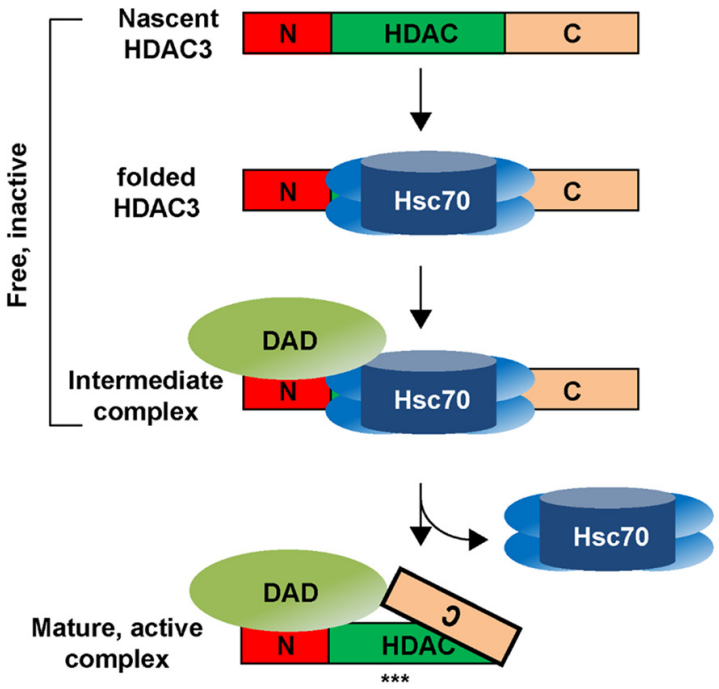

Figure 2. A hypothetical model of HDAC3 activation by corepressors. In the inactive state, HDAC3 is complexed with Hsc70 and TRiC chaperones. Corepressors bind to HDAC3 N-terminus through the DAD domain. The DAD-triggered HDAC3 activation occurs in a stepwise fashion and involves the formation of an intermediate DAD-HDAC3-chaperone complex, whose subsequent conversion into the mature, active state requires a C-terminus dependent conformational change to dissociate chaperones. "***" denotes exposed HDAC3 active site.

but retains the ability to bind to corepressors can rescue the HDAC3-null defect in liver, indicating that HDAC activity is not required for all HDAC3 functions, but its interaction with corepressors such as NCoR is critical. This would challenge the rationale of using traditionally-developed HDAC inhibitors that target the active site of HDACs to inhibit the function of HDAC3 (and possibly other HDACs) in cancers. Nevertheless, the above-mentioned strategy of using inhibitors to prevent the formation of stable HDAC3-corepressor complexes would continue to be warranted in targeting HDAC3 function in cancers.

It has been shown that the inactive form of HDAC3 is in complexes with Hsc70 and TRiC chaperones [139]. These chaperones are released from HDAC3 in its mature form after corepressor association. A recent work has shown that knockdown of NCoR and SMRT in cultured cells reduces the steady-state protein expression of HDAC3 in all tested cell types including colon, prostate and breast cancer cells [175], indicating that the E3 ligase-driven HDAC3 degradation pathway is still intact in cancer cells. Elucidating the nature of HDAC3-specific E3 ligases may offer a new approach to target HDAC3 in cancer cells. It is noteworthy that the steady-state level of liver HDAC3 in the above-mentioned DAD mutant knock-in mice does not differ significantly from the control mice. The difference between living animals and cultured cell may be caused by the use of different assay conditions. Alternatively, the mice may have been forced to compensate for the loss of HDAC3 given that HDAC3 is required for the early embryonic development.

Previous studies have suggested that the C-terminus of HDAC3 is required for its interaction with CoR [140, 171]. Surprisingly, it was shown that if proteasomal activity is blocked, a C-terminus-truncated HDAC3 can still form a complex with CoR in cells [175]. Proteasome-dependent rapid turnover thus may explain earlier failures to detect an interaction between CoR and the C-terminus-truncated HDAC3. Despite the binding to CoR, the C-terminus-truncated HDAC3 remains associated with chaperones and cannot be activated. These data are consistent with a novel function for HDAC3 C-terminus in coupling CoR binding, chaperone dismissal, and subsequent activation and stabilization of HDAC3, suggesting that the C-terminus acts at a step after the binding of corepressors to facilitate the release of chaperones from HDAC3 (**Figure 2**). A role for C-terminus in regulating HDAC3 activity is also supported by the finding that phosphorylation of the conserved C-terminal residue S424 increases the activity of HDAC3 [176]. A recent work reported the 3D structure of a complex containing a C-terminus-truncated HDAC3 and SMRT-DAD [177]. It is worth noting that the C-terminus is cleaved after the formation of the complex, consistent with its role involved in the complex formation and HDAC3 activation.

TBL1 and TBLR1: TBL1 is a protein initially found to play a role in the X-linked late-onset deafness in human [178]. Its counterpart in fly, ebi, has been shown to play a role in fly eye development by regulating the EGF receptor-mediated signaling pathways [179]. Interestingly, Lazar and Wong groups later discovered that TBL1 is a stoichiometric subunit of NCoR and SMRT nuclear receptor corepressor complexes [30, 44]. TBL1 directly interacts with histone tails and facilitates the function of HDAC3 [30, 44]. By purifying FLAG-NCoR and FLAG-HDAC3 interacting proteins, Zhang et al. discovered a TBL1-like protein, which they named TBLR1 (TBL1-like protein 1) [28]. TBLR1/TBL1, like NCoR and SMRT, are the alternative subunits of CoR/HDAC3 corepressor complexes. Interestingly, the expression of TBLR1 is reduced in mature hematopoietic cells compared to progenitor cells [180], suggesting a role for TBLR1 in regulating cell differentiation.

Both TBL1 and TBLR1 have been shown to have "coactivator" functions. Although the classical Gal4-fusion assay failed to support an "activation domain" in TBL1/TBLR1, it confirmed that TBL1/TBLR1 harbor transferable repression domains [30, 44]. This shows that TBL1/TBLR1 are not classical coactivators. The "coactivator" activity of TBL1/TBLR1 appears to be attributed to their ability to drive proteasomal degradation of NCoR/SMRT and CtBP corepressors in a signal-dependent fashion [181]. Perissi et al. showed that TBL1/TBLR1 promote the clearance of NCoR/SMRT and CtBP corepressors by recruiting 19S proteasome particles to drive the ubiquitination and degradation of NCoR/SMRT and CtBP, thus allowing the recruitment of coactivators. This takes place not only on NRs but also on c-Jun and NF-κB binding sites of affected genes [181, 182]. Phosphorylation of TBL1 and TBLR1 on specific residues is required to activate their E3 ligase activities. TBL1 and TBLR1 have imperfect F-boxes. Therefore, an interesting model is that these proteins normally reside in the NCoR/SMRT complex in the inactive state. Phosphorylation and/or possibly other post-translational modifications activate their latent E3 ligase activities, leading to degradation of the corepressors.

Dysregulation of Wnt-β-catenin signaling pathway has been associated with tumorigenesis. Another form of post-translational modifications on TBL1/TBLR1, SUMOylation, has been shown to dissociate TBL1/TBLR1 from the NCoR complex, and subsequently allow them to complex with β-catenin to dock on and activate the promoter of Wnt target genes, which is important for the tumorigenicity of SW480 colon cancer cells [183]. These results suggest that the nature of post-translational modification of TBL1 and TBLR1 determines whether they may function as tumor suppressors or as oncogenes to facilitate repression or activation of context-dependent target genes.

A recent development has implicated TBLR1 involvement in AR regulation and prostate cancer progression. TBLR1 is found to be primarily localized in the nucleus of benign prostate cells and the level is reduced in prostate cancer cells. TBLR1 binds to AR and potentiates AR-dependent transcription of target genes in a phosphorylation- and 19S proteasome-dependent manner. Interestingly, TBLR1 selectively activates genes important for growth suppression and differentiation but not pro-proliferative AR target genes, suggesting a tumor suppressor function of TBLR1 in prostate cancer [184].

GPS2: In search for proteins that can rescue the lethal phenotype of yeast harboring a dominant active yeast Gβγ mutant, Spain et al. have discovered GPS2 as a G-protein pathway suppressor and shown that GPS2 can suppress RAS/MAPK-dependent JNK activation [185]. Another group independently found that GPS2 interacts with Tax, a human T-cell lymphotrophic virus transcription factor, and suppresses TNFalpha-dependent activation of the JNK pathway [186]. Biochemical purification of novel NCoR/HDAC3-interacting proteins identified GPS2 as an integral component of the NCoR/SMRT/HDAC3 complex [28]. A coiled-coil region of GPS2 (amino acids 1-105) directly interacts with the N-terminal regions of both NCoR/SMRT and TBL1/TBLR1 to form a heterotrimeric complex. A recent structural study has confirmed these domain interactions and also shown that TBL1 is organized into a tetrameric structure [31].

Since the discovery of GPS2 as a G-protein pathway suppressor, GPS2 has emerged as a multifunctional protein. GPS2 can act both as a corepressor and a coactivator for various transcription factors including nuclear receptors [187-194], consistent with the presence of distinct repression and activation domains in

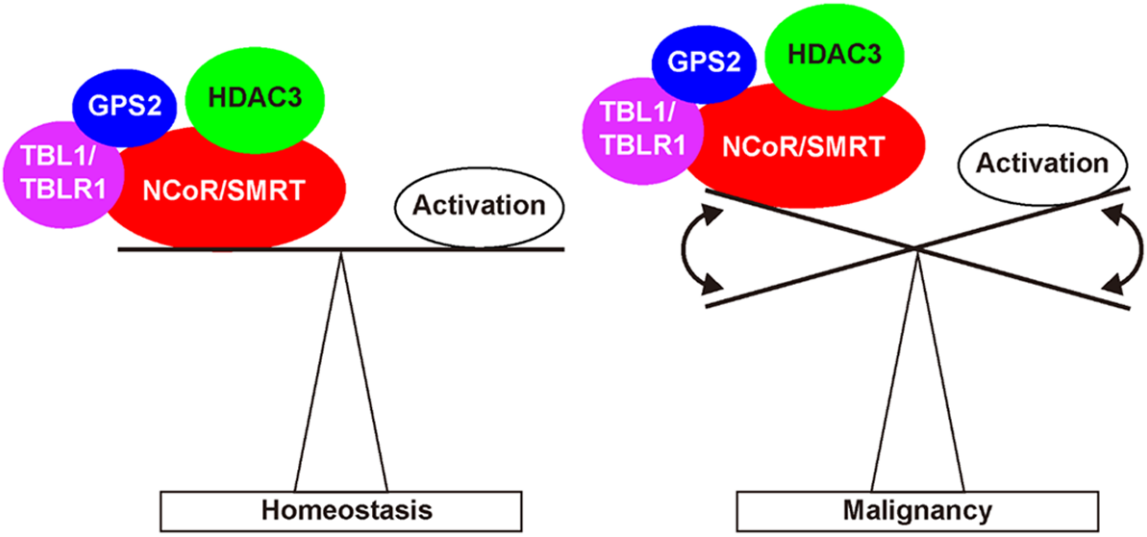

Figure 3. A working model showing that deregulated function of the corepressor complex disrupts homeostatic balance of cellular pathways to promote cancer progression.

GPS2 [28, 187]. Consistent with its coactivator function, GPS2 has also been shown to facilitate histone demethylation of certain target genes [189, 195]. These pro-activation activities of GPS2 may be independent of its interactions with NCoR/SMRT and TBL1/TBLR1. In the context of repression, it has been proposed that GPS2 may, analogous to NCoR/SMRT, tether the corepressor complex to sequence-specific transcription factors. While this idea is still interesting, and in fact is consistent with the reported anti-inflammatory function of GPS2 [196], the nature of transcription factors that use GPS2 to recruit the CoR complex, and the corresponding target genes regulated by the transcription factors, remain to be determined.

Several recent studies have provided evidence that the interaction between GPS2 and CoRs may be a drugable target in cancer. Bi et al. [197] reported that GPS2 is SUMOylated at K45 and K71 within the coiled-coil region that interacts with CoRs. SUMOylation increases the corepressor function of GPS2 for ERα-mediated transcription, initially reported by Cheng et al. [194], in both MCF-7 and T47D breast cancer cells due to enhanced GPS2 incorporation into the TBL1/SMRT complex, which correlates with reduced proliferation of MCF-7 and T47D cells.

Two recent studies reported somatic mutations of GPS2 in a form of aggressive brain tumor, Medulloblastoma [198]. These mutations affect the residues in the coiled-coil region of GPS2 that mediate its interaction with NCoR/SMRT and TBL1/TBLR1. The mutations significantly worsen the prognosis [199]. The impact of these mutations on the GPS2-CoR interaction has yet to be studied. Given the anti-inflammatory function of GPS2, one may speculate that such mutations may reduce the ability of the corepressor complex to suppress cytokine-dependent signaling pathways, which may predispose the affected cells to oncogenesis.

GPS2 turns out to be the first CoR complex subunit that forms fusion proteins with different partners in cancers. Undifferentiated spindle cell sarcoma (UDS) is a type of cancer with poorly defined diagnostic markers. O'Meara et al. identified a novel chromosomal translocation t(17;19)(p13;q13) in a pediatric UDS [200]. Interestingly, this in-frame fusion is between GPS2 and MLL4, which is the active subunit of one of the histone H3K4 methyltransferase complexes [201]. This fusion is oncogenic because it promotes anchorage-independent growth of the cells. It will be interesting to determine whether the fusion protein-containing complexes show multiple histone modification activities conferred by MLL4 (methyltransferase) and GPS2 (deacetylase and/or demethylase), which may be important for deregulation of gene expression in tumors. Besides MLL4, GPS2 has also been reported to fuse to other

proteins in a prostate carcinoma cell line [202] and in glioblastoma multiforme [203]. These findings underscore the emerging important role of GPS2 in cancer.

Conclusion and future directions

Since the discovery of NCoR/SMRT nearly 20 years ago, tremendous progress has been made in understanding the mechanisms, regulation and functions of NCoR/SMRT and their interacting proteins in transcription, and their involvement in diverse pathways that regulate metabolism, inflammation and oncogenesis. A major advance in the field is the discovery of the multi-protein complex containing NCoR/SMRT, HDAC3, TBL1/TBLR1 and GPS2. However, to date, we still do not fully understand how these proteins regulate transcription in normal and cancer cells. Future studies may be devoted to understanding (i) the specificity of NCoR, SMRT, and their different isoforms, (ii) how the free form of HDAC3 assembles into the mature NCoR/SMRT-HDAC3 complex, (iii) the mechanism of "coactivator" functions of TBL1/TBLR1 and GPS2 and how these functions may be related to their interactions with NCoR/SMRT, (iv) the regulation of the expression of these proteins in normal and cancer cells, and (v) the genome-wide targets of these proteins. While the literature has supported the concept that deregulated corepressor function facilitates cancer development by disrupting the homeostatic balance between corepressors and coactivators (or other regulatory proteins) in the regulation of chromatin structure, transcription, DNA repair, inflammation and other important biological processes (**Figure 3**), corepressors may have different mechanisms and play either pro- or anti-tumorigenic roles in different types of cancers and leukemias. It is thus important to fully understand the context-dependent function of corepressors. Given the direct interactions between the various corepressor components and the transcription factors (such as ER, AR and leukemia fusion proteins) involved in cancers and leukemias, these corepressor proteins should serve as important drugable targets for cancer therapy.

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Disclosure of conflict of interest

None.

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References

[1] Glass CK and Rosenfeld MG. The coregulator exchange in transcriptional functions of nuclear receptors. Genes Dev 2000; 14: 121-141.

[2] Horlein AJ, Naar AM, Heinzel T, Torchia J, Gloss B, Kurokawa R, Ryan A, Kamei Y, Soderstrom M, Glass CK and Rosenfeld MG. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. Nature 1995; 377: 397-404.

[3] Chen JD and Evans RM. A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature 1995; 377: 454-457.

[4] Baniahmad A, Köhne AC, Renkawitz R. A transferable silencing domain is present in the thyroid hormone receptor, in the v-erbA oncogene product and in the retinoic acid receptor. EMBO J 1992; 11: 1015-1023.

[5] Tong GX, Jeyakumar M, Tanen MR and Bagchi MK. Transcriptional silencing by unliganded thyroid hormone receptor beta requires a soluble corepressor that interacts with the ligand-binding domain of the receptor. Mol Cell Biol 1996; 16: 1909-1920.

[6] Zhang J and Lazar MA. The mechanism of action of thyroid hormones. Annu Rev Physiol 2000; 62: 439-466.

[7] Ordentlich P, Downes M, Xie W, Genin A, Spinner NB and Evans RM. Unique forms of human and mouse nuclear receptor corepressor SMRT. Proc Natl Acad Sci U S A 1999; 96: 2639-2644.

[8] Park EJ, Schroen DJ, Yang M, Li H, Li L and Chen JD. SMRTe, a silencing mediator for retinoid and thyroid hormone receptors-extended isoform that is more related to the nuclear receptor corepressor. Proc Natl Acad Sci U S A 1999; 96: 3519-3524.

[9] Dwivedi PP, Muscat GE, Bailey PJ, Omdahl JL and May BK. Repression of basal transcription by vitamin D receptor: evidence for interaction of unliganded vitamin D receptor with two receptor interaction domains in RIP13delta1. J Mol Endocrinol 1998; 20: 327-335.

[10] Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevrivy DJ and Leid M. Identification of nuclear receptor corepressor as a peroxisome proliferator-activated receptor alpha interacting protein. J Biol Chem 1999; 274: 15901-15907.
[11] Wagner BL, Valledor AF, Shao G, Daige CL, Bischoff ED, Petrowski M, Jepsen K, Baek SH, Heyman RA, Rosenfeld MG, Schulman IG and Glass CK. Promoter-specific roles for liver X receptor/corepressor complexes in the regulation of ABCA1 and SREBP1 gene expression. Mol Cell Biol 2003; 23: 5780-5789.
[12] Harding HP and Lazar MA. The monomer-binding orphan receptor Rev-Erb represses transcription as a dimer on a novel direct repeat. Mol Cell Biol 1995; 15: 4791-4802.
[13] Zamir I, Harding HP, Atkins GB, Horlein A, Glass CK, Rosenfeld MG and Lazar MA. A nuclear hormone receptor corepressor mediates transcriptional silencing by receptors with distinct repression domains. Mol Cell Biol 1996; 16: 5458-5465.
[14] Shibata H, Nawaz Z, Tsai SY, O'Malley BW and Tsai MJ. Gene silencing by chicken ovalbumin upstream promoter-transcription factor I (COUP-TFI) is mediated by transcriptional corepressors, nuclear receptor-corepressor (N-CoR) and silencing mediator for retinoic acid receptor and thyroid hormone receptor (SMRT). Mol Endocrinol 1997; 11: 714-724.
[15] Crawford PA, Dorn C, Sadovsky Y and Milbrandt J. Nuclear receptor DAX-1 recruits nuclear receptor corepressor N-CoR to steroidogenic factor 1. Mol Cell Biol 1998; 18: 2949-2956.
[16] Shang Y, Hu X, DiRenzo J, Lazar MA and Brown M. Cofactor dynamics and sufficiency in estrogen receptor-regulated transcription. Cell 2000; 103: 843-852.
[17] Dotzlaw H, Moehren U, Mink S, Cato AC, Iniguez Lluhi JA and Baniahmad A. The amino terminus of the human AR is target for corepressor action and antihormone agonism. Mol Endocrinol 2002; 16: 661-673.
[18] Liao G, Chen LY, Zhang A, Godavarthy A, Xia F, Ghosh JC, Li H and Chen JD. Regulation of androgen receptor activity by the nuclear receptor corepressor SMRT. J Biol Chem 2003; 278: 5052-5061.
[19] Zhang X, Jeyakumar M, Petukhov S and Bagchi MK. A nuclear receptor corepressor modulates transcriptional activity of antagonist-occupied steroid hormone receptor. Mol Endocrinol 1998; 12: 513-524.
[20] Liu XF and Bagchi MK. Recruitment of distinct chromatin-modifying complexes by tamoxifen-complexed estrogen receptor at natural target gene promoters in vivo. J Biol Chem 2004; 279: 15050-15058.
[21] Hu X and Lazar MA. The CoRNR motif controls the recruitment of corepressors by nuclear hormone receptors. Nature 1999; 402: 93-96.
[22] Perissi V, Staszewski LM, McInerney EM, Kurokawa R, Krones A, Rose DW, Lambert MH, Milburn MV, Glass CK and Rosenfeld MG. Molecular determinants of nuclear receptor-corepressor interaction. Genes Dev 1999; 13: 3198-3208.
[23] Nagy L, Kao HY, Love JD, Li C, Banayo E, Gooch JT, Krishna V, Chatterjee K, Evans RM and Schwabe JW. Mechanism of corepressor binding and release from nuclear hormone receptors. Genes Dev 1999; 13: 3209-3216.
[24] Heery DM, Kalkhoven E, Hoare S and Parker MG. A signature motif in transcriptional co-activators mediates binding to nuclear receptors. Nature 1997; 387: 733-736.
[25] Webb P, Anderson CM, Valentine C, Nguyen P, Marimuthu A, West BL, Baxter JD and Kushner PJ. The nuclear receptor corepressor (N-CoR) contains three isoleucine motifs (I/LXXII) that serve as receptor interaction domains (IDs). Mol Endocrinol 2000; 14: 1976-1985.
[26] Cohen RN, Brzostek S, Kim B, Chorev M, Wondisford FE and Hollenberg AN. The specificity of interactions between nuclear hormone receptors and corepressors is mediated by distinct amino acid sequences within the interacting domains. Mol Endocrinol 2001; 15: 1049-1061.
[27] Hu X, Li Y and Lazar MA. Determinants of CoRNR-dependent repression complex assembly on nuclear hormone receptors. Mol Cell Biol 2001; 21: 1747-1758.
[28] Zhang J, Kalkum M, Chait BT and Roeder RG. The N-CoR-HDAC3 nuclear receptor corepressor complex inhibits the JNK pathway through the integral subunit GPS2. Mol Cell 2002; 9: 611-623.
[29] Li J, Wang J, Nawaz Z, Liu JM, Qin J and Wong J. Both corepressor proteins SMRT and N-CoR exist in large protein complexes containing HDAC3. EMBO J 2000; 19: 4342-4350.
[30] Guenther MG, Lane WS, Fischle W, Verdin E, Lazar MA and Shiekhattar R. A core SMRT corepressor complex containing HDAC3 and TBL1, a WD40-repeat protein linked to deafness. Genes Dev 2000; 14: 1048-1057.
[31] Oberoi J, Fairall L, Watson PJ, Yang JC, Czimmerer Z, Kampmann T, Goult BT, Greenwood JA, Gooch JT, Kallenberger BC, Nagy L, Neuhaus D and Schwabe JW. Structural basis for the assembly of the SMRT/NCoR core transcriptional repression machinery. Nat Struct Mol Biol 2011; 18: 177-184.
[32] Zhang Y, Iratni R, Erdjument-Bromage H, Tempst P and Reinberg D. Histone deacetylases

and SAP18, a novel polypeptide, are components of a human Sin3 complex. Cell 1997; 89: 357-364.
[33] Zhang Y, Sun ZW, Iratni R, Erdjument-Bromage H, Tempst P, Hampsey M and Reinberg D. SAP30, a novel protein conserved between human and yeast, is a component of a histone deacetylase complex. Mol Cell 1998; 1: 1021-1031.
[34] Jones PL, Sachs LM, Rouse N, Wade PA and Shi YB. Multiple N-CoR complexes contain distinct histone deacetylases. J Biol Chem 2001; 276: 8807-8811.
[35] Alland L, Muhle R, Hou H Jr, Potes J, Chin L, Schreiber-Agus N and DePinho RA. Role for N-CoR and histone deacetylase in Sin3-mediated transcriptional repression. Nature 1997; 387: 49-55.
[36] Heinzel T, Lavinsky RM, Mullen TM, Soderstrom M, Laherty CD, Torchia J, Yang WM, Brard G, Ngo SD, Davie JR, Seto E, Eisenman RN, Rose DW, Glass CK and Rosenfeld MG. A complex containing N-CoR, mSin3 and histone deacetylase mediates transcriptional repression. Nature 1997; 387: 43-48.
[37] Nagy L, Kao HY, Chakravarti D, Lin RJ, Hassig CA, Ayer DE, Schreiber SL and Evans RM. Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase. Cell 1997; 89: 373-380.
[38] Huang EY, Zhang J, Miska EA, Guenther MG, Kouzarides T and Lazar MA. Nuclear receptor corepressors partner with class II histone deacetylases in a Sin3-independent repression pathway. Genes Dev 2000; 14: 45-54.
[39] Kao HY, Downes M, Ordentlich P and Evans RM. Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression. Genes Dev 2000; 14: 55-66.
[40] Underhill C, Qutob MS, Yee SP and Torchia J. A novel nuclear receptor corepressor complex, N-CoR, contains components of the mammalian SWI/SNF complex and the corepressor KAP-1. J Biol Chem 2000; 275: 40463-40470.
[41] Cowger JJ and Torchia J. Direct association between the CREB-binding protein (CBP) and nuclear receptor corepressor (N-CoR). Biochemistry (Mosc) 2006; 45: 13150-13162.
[42] Jepsen K and Rosenfeld MG. Biological roles and mechanistic actions of co-repressor complexes. J Cell Sci 2002; 115: 689-698.
[43] Rosenfeld MG, Lunyak VV and Glass CK. Sensors and signals: a coactivator/corepressor/epigenetic code for integrating signal-dependent programs of transcriptional response. Genes Dev 2006; 20: 1405-1428.
[44] Yoon HG, Chan DW, Huang ZQ, Li J, Fondell JD, Qin J, Wong J. Purification and functional characterization of the human N-CoR complex: the roles of HDAC3, TBL1 and TBLR1. EMBO J 2003; 22: 1336-1346.
[45] Varlakhanova N, Snyder C, Jose S, Hahm JB and Privalsky ML. Estrogen receptors recruit SMRT and N-CoR corepressors through newly recognized contacts between the corepressor N terminus and the receptor DNA binding domain. Mol Cell Biol 2010; 30: 1434-1445.
[46] Aasland R, Stewart AF and Gibson T. The SANT domain: a putative DNA-binding domain in the SWI-SNF and ADA complexes, the transcriptional co-repressor N-CoR and TFIIIB. Trends Biochem Sci 1996; 21: 87-88.
[47] Codina A, Love JD, Li Y, Lazar MA, Neuhaus D and Schwabe JW. Structural insights into the interaction and activation of histone deacetylase 3 by nuclear receptor corepressors. Proc Natl Acad Sci U S A 2005; 102: 6009-6014.
[48] Ishizuka T and Lazar MA. The nuclear receptor corepressor deacetylase activating domain is essential for repression by thyroid hormone receptor. Mol Endocrinol 2005; 19: 1443-1451.
[49] Adikesavan AK, Karmakar S, Pardo P, Wang L, Liu S, Li W and Smith CL. Activation of p53 transcriptional activity by SMRT: a histone deacetylase 3-independent function of a transcriptional corepressor. Mol Cell Biol 2014; 34: 1246-1261.
[50] Peterson TJ, Karmakar S, Pace MC, Gao T and Smith CL. The silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) corepressor is required for full estrogen receptor alpha transcriptional activity. Mol Cell Biol 2007; 27: 5933-5948.
[51] Boyer LA, Langer MR, Crowley KA, Tan S, Denu JM and Peterson CL. Essential role for the SANT domain in the functioning of multiple chromatin remodeling enzymes. Mol Cell 2002; 10: 935-942.
[52] Yu J, Li Y, Ishizuka T, Guenther MG and Lazar MA. A SANT motif in the SMRT corepressor interprets the histone code and promotes histone deacetylation. EMBO J 2003; 22: 3403-3410.
[53] Hartman HB, Yu J, Alenghat T, Ishizuka T and Lazar MA. The histone-binding code of nuclear receptor co-repressors matches the substrate specificity of histone deacetylase 3. EMBO Rep 2005; 6: 445-451.
[54] Yoon HG, Choi Y, Cole PA and Wong J. Reading and function of a histone code involved in targeting corepressor complexes for repression. Mol Cell Biol 2005; 25: 324-335.
[55] Karagianni P and Wong J. HDAC3: taking the SMRT-N-CoRrect road to repression. Oncogene 2007; 26: 5439-5449.
[56] Barish GD, Yu RT, Karunasiri MS, Becerra D, Kim J, Tseng TW, Tai LJ, Leblanc M, Diehl C,

Cerchietti L, Miller YI, Witztum JL, Melnick AM, Dent AL, Tangirala RK and Evans RM. The Bcl6-SMRT/NCoR cistrome represses inflammation to attenuate atherosclerosis. Cell Metab 2012; 15: 554-562.
[57] Huang C, Hatzi K and Melnick A. Lineage-specific functions of Bcl-6 in immunity and inflammation are mediated by distinct biochemical mechanisms. Nat Immunol 2013; 14: 380-388.
[58] Dhordain P, Lin RJ, Quief S, Lantoine D, Kerckaert JP, Evans RM and Albagli O. The LAZ3 (BCL-6) oncoprotein recruits a SMRT/mSIN3A/histone deacetylase containing complex to mediate transcriptional repression. Nucleic Acids Res 1998; 26: 4645-4651.
[59] Wong CW and Privalsky ML. Components of the SMRT corepressor complex exhibit distinctive interactions with the POZ domain oncoproteins PLZF, PLZF-RARalpha, and BCL-6. J Biol Chem 1998; 273: 27695-27702.
[60] Bailey P, Downes M, Lau P, Harris J, Chen SL, Hamamori Y, Sartorelli V and Muscat GE. The nuclear receptor corepressor N-CoR regulates differentiation: N-CoR directly interacts with MyoD. Mol Endocrinol 1999; 13: 1155-1168.
[61] Iso T, Sartorelli V, Poizat C, Iezzi S, Wu HY, Chung G, Kedes L and Hamamori Y. HERP, a novel heterodimer partner of HES/E(spl) in Notch signaling. Mol Cell Biol 2001; 21: 6080-6089.
[62] Scully KM JE, Jepsen K, Lunyak V, Viadiu H, Carrière C, Rose DW, Hooshmand F, Aggarwal AK, Rosenfeld MG. Allosteric effects of Pit-1 DNA sites on long-term repression in cell type specification. Science 2000; 290: 1127-1131.
[63] Xu L, Lavinsky RM, Dasen JS, Flynn SE, McInerney EM, Mullen TM, Heinzel T, Szeto D, Korzus E, Kurokawa R, Aggarwal AK, Rose DW, Glass CK and Rosenfeld MG. Signal-specific co-activator domain requirements for Pit-1 activation. Nature 1998; 395: 301-306.
[64] Kakizawa T, Miyamoto T, Ichikawa K, Takeda T, Suzuki S, Mori J, Kumagai M, Yamashita K and Hashizume K. Silencing mediator for retinoid and thyroid hormone receptors interacts with octamer transcription factor-1 and acts as a transcriptional repressor. J Biol Chem 2001; 276: 9720-9725.
[65] Kao HY, Ordentlich P, Koyano-Nakagawa N, Tang Z, Downes M, Kintner CR, Evans RM and Kadesch T. A histone deacetylase corepressor complex regulates the Notch signal transduction pathway. Genes Dev 1998; 12: 2269-2277.
[66] Oswald F, Kostezka U, Astrahantseff K, Bourteele S, Dillinger K, Zechner U, Ludwig L, Wilda M, Hameister H, Knochel W, Liptay S and Schmid RM. SHARP is a novel component of the Notch/RBP-Jkappa signalling pathway. EMBO J 2002; 21: 5417-5426.
[67] Zhou S and Hayward SD. Nuclear localization of CBF1 is regulated by interactions with the SMRT corepressor complex. Mol Cell Biol 2001; 21: 6222-6232.
[68] Asahara H, Dutta S, Kao HY, Evans RM and Montminy M. Pbx-Hox heterodimers recruit coactivator-corepressor complexes in an isoform-specific manner. Mol Cell Biol 1999; 19: 8219-8225.
[69] Saleh M, Rambaldi I, Yang XJ and Featherstone MS. Cell signaling switches HOX-PBX complexes from repressors to activators of transcription mediated by histone deacetylases and histone acetyltransferases. Mol Cell Biol 2000; 20: 8623-8633.
[70] Lee SK, Na SY, Jung SY, Choi JE, Jhun BH, Cheong J, Meltzer PS, Lee YC and Lee JW. Activating protein-1, nuclear factor-kappaB, and serum response factor as novel target molecules of the cancer-amplified transcription coactivator ASC-2. Mol Endocrinol 2000; 14: 915-925.
[71] Baek SH, Ohgi KA, Rose DW, Koo EH, Glass CK and Rosenfeld MG. Exchange of N-CoR corepressor and Tip60 coactivator complexes links gene expression by NF-kappaB and beta-amyloid precursor protein. Cell 2002; 110: 55-67.
[72] Espinosa L, Santos S, Ingles-Esteve J, Munoz-Canoves P and Bigas A. p65-NFkappaB synergizes with Notch to activate transcription by triggering cytoplasmic translocation of the nuclear receptor corepressor N-CoR. J Cell Sci 2002; 115: 1295-1303.
[73] Espinosa L, Ingles-Esteve J, Robert-Moreno A and Bigas A. IkappaBalpha and p65 regulate the cytoplasmic shuttling of nuclear corepressors: cross-talk between Notch and NFkappaB pathways. Mol Biol Cell 2003; 14: 491-502.
[74] Jang MK, Goo YH, Sohn YC, Kim YS, Lee SK, Kang H, Cheong J and Lee JW. Ca2+/calmodulin-dependent protein kinase IV stimulates nuclear factor-kappa B transactivation via phosphorylation of the p65 subunit. J Biol Chem 2001; 276: 20005-20010.
[75] Hong SH, David G, Wong CW, Dejean A and Privalsky ML. SMRT corepressor interacts with PLZF and with the PML-retinoic acid receptor alpha (RARalpha) and PLZF-RARalpha oncoproteins associated with acute promyelocytic leukemia. Proc Natl Acad Sci U S A 1997; 94: 9028-9033.
[76] He LZ, Guidez F, Tribioli C, Peruzzi D, Ruthardt M, Zelent A and Pandolfi PP. Distinct interactions of PML-RARalpha and PLZF-RARalpha with co-repressors determine differential responses to RA in APL. Nat Genet 1998; 18: 126-135.

[77] Gelmetti V, Zhang J, Fanelli M, Minucci S, Pelicci PG and Lazar MA. Aberrant recruitment of the nuclear receptor corepressor-histone deacetylase complex by the acute myeloid leukemia fusion partner ETO. Mol Cell Biol 1998; 18: 7185-7191.

[78] Lutterbach B, Westendorf JJ, Linggi B, Patten A, Moniwa M, Davie JR, Huynh KD, Bardwell VJ, Lavinsky RM, Rosenfeld MG, Glass C, Seto E, Hiebert SW. ETO, a target of t(8;21) in acute leukemia, interacts with the N-CoR and mSin3 corepressors. Mol Cell Biol 1998; 18: 7176-7184.

[79] Wang J, Hoshino T, Redner RL, Kajigaya S and Liu JM. ETO, fusion partner in t(8;21) acute myeloid leukemia, represses transcription by interaction with the human N-CoR/mSin3/HDAC1 complex. Proc Natl Acad Sci U S A 1998; 95: 10860-10865.

[80] Luo K, Stroschein SL, Wang W, Chen D, Martens E, Zhou S and Zhou Q. The Ski oncoprotein interacts with the Smad proteins to repress TGFbeta signaling. Genes Dev 1999; 13: 2196-2206.

[81] Li X and McDonnell DP. The transcription factor B-Myb is maintained in an inhibited state in target cells through its interaction with the nuclear corepressors N-CoR and SMRT. Mol Cell Biol 2002; 22: 3663-3673.

[82] Nguyen TA, Hoivik D, Lee JE and Safe S. Interactions of nuclear receptor coactivator/corepressor proteins with the aryl hydrocarbon receptor complex. Arch Biochem Biophys 1999; 367: 250-257.

[83] Shi Y, Downes M, Xie W, Kao HY, Ordentlich P, Tsai CC, Hon M and Evans RM. Sharp, an inducible cofactor that integrates nuclear receptor repression and activation. Genes Dev 2001; 15: 1140-1151.

[84] Yoon HG, Chan DW, Reynolds AB, Qin J and Wong J. N-CoR Mediates DNA Methylation-Dependent Repression through a Methyl CpG Binding Protein Kaiso. Mol Cell 2003; 12: 723-734.

[85] Ebert DH, Gabel HW, Robinson ND, Kastan NR, Hu LS, Cohen S, Navarro AJ, Lyst MJ, Ekiert R, Bird AP and Greenberg ME. Activity-dependent phosphorylation of MeCP2 threonine 308 regulates interaction with NCoR. Nature 2013; 499: 341-345.

[86] Fu J, Yoon HG, Qin J and Wong J. Regulation of P-TEFb elongation complex activity by CDK9 acetylation. Mol Cell Biol 2007; 27: 4641-4651.

[87] Wang Z, Zang C, Cui K, Schones DE, Barski A, Peng W and Zhao K. Genome-wide mapping of HATs and HDACs reveals distinct functions in active and inactive genes. Cell 2009; 138: 1019-1031.

[88] Dobrzycka KM, Townson SM, Jiang S and Oesterreich S. Estrogen receptor corepressors -- a role in human breast cancer? Endocr Relat Cancer 2003; 10: 517-536.

[89] Ciriello G, Sinha R, Hoadley KA, Jacobsen AS, Reva B, Perou CM, Sander C, Schultz N. The molecular diversity of Luminal A breast tumors. Breast Cancer Res Treat 2013; 141: 409-420.

[90] Kurebayashi J, Otsuki T, Kunisue H, Tanaka K, Yamamoto S and Sonoo H. Expression levels of estrogen receptor-alpha, estrogen receptor-beta, coactivators, and corepressors in breast cancer. Clin Cancer Res 2000; 6: 512-518.

[91] Heldring N, Pawson T, McDonnell D, Treuter E, Gustafsson JA and Pike AC. Structural insights into corepressor recognition by antagonist-bound estrogen receptors. J Biol Chem 2007; 282: 10449-10455.

[92] Smith CL, Nawaz Z and O'Malley BW. Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. Mol Endocrinol 1997; 11: 657-666.

[93] Brzozowski AM, Pike AC, Dauter Z, Hubbard RE, Bonn T, Engstrom O, Ohman L, Greene GL, Gustafsson JA and Carlquist M. Molecular basis of agonism and antagonism in the oestrogen receptor. Nature 1997; 389: 753-758.

[94] Shiau AK, Barstad D, Loria PM, Cheng L, Kushner PJ, Agard DA and Greene GL. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell 1998; 95: 927-937.

[95] Graham JD, Bain DL, Richer JK, Jackson TA, Tung L, Horwitz KB. Nuclear receptor conformation, coregulators, and tamoxifen-resistant breast cancer. Steroids 2000; 65: 579-584.

[96] Zhang J, Guenther MG, Carthew RW and Lazar MA. Proteasomal regulation of nuclear receptor corepressor-mediated repression. Genes Dev 1998; 12: 1775-1780.

[97] Frasor J, Danes JM, Funk CC and Katzenellenbogen BS. Estrogen down-regulation of the corepressor N-CoR: mechanism and implications for estrogen derepression of N-CoR-regulated genes. Proc Natl Acad Sci U S A 2005; 102: 13153-13157.

[98] Jansen MP, Ruigrok-Ritstier K, Dorssers LC, van Staveren IL, Look MP, Meijer-van Gelder ME, Sieuwerts AM, Helleman J, Sleijfer S, Klijn JG, Foekens JA and Berns EM. Downregulation of SIAH2, an ubiquitin E3 ligase, is associated with resistance to endocrine therapy in breast cancer. Breast Cancer Res Treat 2009; 116: 263-271.

[99] Interiano RB, Yang J, Harris AL and Davidoff AM. Seven In Absentia Homolog 2 (SIAH2) downregulation is associated with tamoxifen

resistance in MCF-7 breast cancer cells. J Surg Res 2014; 190: 203-209.
[100] Stanya KJ, Liu Y, Means AR and Kao HY. Cdk2 and Pin1 negatively regulate the transcriptional corepressor SMRT. J Cell Biol 2008; 183: 49-61.
[101] De Amicis F, Zupo S, Panno ML, Malivindi R, Giordano F, Barone I, Mauro L, Fuqua SA and Ando S. Progesterone receptor B recruits a repressor complex to a half-PRE site of the estrogen receptor alpha gene promoter. Mol Endocrinol 2009; 23: 454-465.
[102] Konduri SD, Medisetty R, Liu W, Kaipparettu BA, Srivastava P, Brauch H, Fritz P, Swetzig WM, Gardner AE, Khan SA and Das GM. Mechanisms of estrogen receptor antagonism toward p53 and its implications in breast cancer therapeutic response and stem cell regulation. Proc Natl Acad Sci U S A 2010; 107: 15081-15086.
[103] Bartella V, Rizza P, Barone I, Zito D, Giordano F, Giordano C, Catalano S, Mauro L, Sisci D, Panno ML, Fuqua SA and Andò S. Estrogen receptor beta binds Sp1 and recruits a corepressor complex to the estrogen receptor alpha gene promoter. Breast Cancer Res Treat 2012; 134: 569-581.
[104] Denmeade SR and Isaacs JT. A history of prostate cancer treatment. Nat Rev Cancer 2002; 2: 389-396.
[105] Salesi N, Carlini P, Ruggeri EM, Ferretti G, Bria E and Cognetti F. Prostate cancer: the role of hormonal therapy. J Exp Clin Cancer Res 2005 24: 175-180.
[106] Burd CJ, Morey LM and Knudsen KE. Androgen receptor corepressors and prostate cancer. Endocr Relat Cancer 2006; 13: 979-994.
[107] Yoon HG and Wong J. The corepressors silencing mediator of retinoid and thyroid hormone receptor and nuclear receptor corepressor are involved in agonist- and antagonist-regulated transcription by androgen receptor. Mol Endocrinol 2006; 20: 1048-1060.
[108] Hodgson MC, Astapova I, Cheng S, Lee LJ, Verhoeven MC, Choi E, Balk SP and Hollenberg AN. The androgen receptor recruits nuclear receptor CoRepressor (N-CoR) in the presence of mifepristone via its N and C termini revealing a novel molecular mechanism for androgen receptor antagonists. J Biol Chem 2005; 280: 6511-6519.
[109] Berrevoets CA, Umar A, Trapman J and Brinkmann AO. Differential modulation of androgen receptor transcriptional activity by the nuclear receptor co-repressor (N-CoR). Biochem J 2004; 379: 731-738.
[110] Laschak M, Bechtel M, Spindler KD and Hessenauer A. Inability of NCoR/SMRT to repress androgen receptor transcriptional activity in prostate cancer cell lines. Int J Mol Med 2011; 28: 645-651.
[111] Choi HK, Yoo JY, Jeong MH, Park SY, Shin DM, Jang SW, Yoon HG and Choi KC. Protein kinase A phosphorylates NCoR to enhance its nuclear translocation and repressive function in human prostate cancer cells. J Cell Physiol 2013; 228: 1159-1165.
[112] Godoy AS, Sotomayor PC, Villagran M, Yacoub R, Montecinos VP, McNerney EM, Moser M, Foster BA and Onate SA. Altered corepressor SMRT expression and recruitment to target genes as a mechanism that change the response to androgens in prostate cancer progression. Biochem Biophys Res Commun 2012; 423: 564-570.
[113] Yoo JY, Lim BJ, Choi HK, Hong SW, Jang HS, Kim C, Chun KH, Choi KC and Yoon HG. CK2-NCoR signaling cascade promotes prostate tumorigenesis. Oncotarget 2013; 4: 972-983.
[114] Qi T, Chen Y, Zhu Y, Jiang J, Wang L and Qi J. Contrast-enhanced transrectal ultrasonography for detection and localization of prostate index tumor: correlation with radical prostatectomy findings. Urology 2014; 84: 138-143.
[115] Grignani F, De Matteis S, Nervi C, Tomassoni L, Gelmetti V, Cioce M, Fanelli M, Ruthardt M, Ferrara FF, Zamir I, Seiser C, Lazar MA, Minucci S and Pelicci PG. Fusion proteins of the retinoic acid receptor-alpha recruit histone deacetylase in promyelocytic leukaemia. Nature 1998; 391: 815-818.
[116] Lin RJ, Nagy L, Inoue S, Shao W, Miller WH Jr and Evans RM. Role of the histone deacetylase complex in acute promyelocytic leukaemia. Nature 1998; 391: 811-814.
[117] Lin RJ, Sternsdorf T, Tini M and Evans RM. Transcriptional regulation in acute promyelocytic leukemia. Oncogene 2001; 20: 7204-7215.
[118] He LZ, Guidez F, Tribioli C, Peruzzi D, Ruthardt M, Zelent A and Pandolfi PP. Distinct interactions of PML-RARalpha and PLZF-RARalpha with co-repressors determine differential responses to RA in APL. Nat Genet 1998; 18: 126-135.
[119] Racanicchi S, Maccherani C, Liberatore C, Billi M, Gelmetti V, Panigada M, Rizzo G, Nervi C and Grignani F. Targeting fusion protein/corepressor contact restores differentiation response in leukemia cells. EMBO J 2005; 24: 1232-1242.
[120] Atsumi A, Tomita A, Kiyoi H, Naoe T. Histone deacetylase 3 (HDAC3) is recruited to target promoters by PML-RARalpha as a component of the N-CoR co-repressor complex to repress transcription in vivo. Biochem Biophys Res Commun 2006; 345: 1471-1480.

[121] Mengeling BJ, Phan TQ, Goodson ML and Privalsky ML. Aberrant corepressor interactions implicated in PML-RAR(alpha) and PLZF-RAR(alpha) leukemogenesis reflect an altered recruitment and release of specific NCoR and SMRT splice variants. J Biol Chem 2011; 286: 4236-4247.

[122] Farris M, Lague A, Manuelyan Z, Statnekov J and Francklyn C. Altered nuclear cofactor switching in retinoic-resistant variants of the PML-RARα oncoprotein of acute promyelocytic leukemia. Proteins 2012; 80: 1095-1099.

[123] Lutterbach B, Westendorf JJ, Linggi B, Patten A, Moniwa M, Davie JR, Huynh KD, Bardwell VJ, Lavinsky RM, Rosenfeld MG, Glass C, Seto E and Hiebert SW. ETO, a target of t(8;21) in acute leukemia, interacts with the N-CoR and mSin3 corepressors. Mol Cell Biol 1998; 18: 7176-7184.

[124] Yan M, Burel SA, Peterson LF, Kanbe E, Iwasaki H, Boyapati A, Hines R, Akashi K and Zhang DE. Deletion of an AML1-ETO C-terminal NcoR/SMRT-interacting region strongly induces leukemia development. Proc Natl Acad Sci U S A 2004; 101: 17186-17191.

[125] Zhang J, Hug BA, Huang EY, Chen CW, Gelmetti V, Maccarana M, Minucci S, Pelicci PG and Lazar MA. Oligomerization of ETO is obligatory for corepressor interaction. Mol Cell Biol 2001; 21: 156-163.

[126] Hug BA and Lazar MA. ETO interacting proteins. Oncogene 2004; 23: 4270-4274.

[127] Gamou T, Kitamura E, Hosoda F, Shimizu K, Shinohara K, Hayashi Y, Nagase T, Yokoyama Y and Ohki M. The partner gene of AML1 in t(16;21) myeloid malignancies is a novel member of the MTG8(ETO) family. Blood 1998; 91: 4028-4037.

[128] Melnick AM, Westendorf JJ, Polinger A, Carlile GW, Arai S, Ball HJ, Lutterbach B, Hiebert SW and Licht JD. The ETO protein disrupted in t(8;21)-associated acute myeloid leukemia is a corepressor for the promyelocytic leukemia zinc finger protein. Mol Cell Biol 2000; 20: 2075-2086.

[129] Linggi B, Muller-Tidow C, van de Locht L, Hu M, Nip J, Serve H, Berdel WE, van der Reijden B, Quelle DE, Rowley JD, Cleveland J, Jansen JH, Pandolfi PP and Hiebert SW. The t(8;21) fusion protein, AML1 ETO, specifically represses the transcription of the p14(ARF) tumor suppressor in acute myeloid leukemia. Nat Med 2002; 8: 743-750.

[130] Zhang J, Kalkum M, Yamamura S, Chait BT and Roeder RG. E protein silencing by the leukemogenic AML1-ETO fusion protein. Science 2004; 305: 1286-1289.

[131] Gow CH, Guo C, Wang D, Hu Q and Zhang J. Differential involvement of E2A-corepressor interactions in distinct leukemogenic pathways. Nucleic Acids Res 2014; 42: 137-152.

[132] Secrist JP, Zhou X and Richon VM. HDAC inhibitors for the treatment of cancer. Curr Opin Investig Drugs 2003; 4: 1422-1427.

[133] Cress WD and Seto E. Histone deacetylases, transcriptional control, and cancer. J Cell Physiol 2000; 184: 1-16.

[134] Kramer OH, Gottlicher M and Heinzel T. Histone deacetylase as a therapeutic target. Trends Endocrinol Metab 2001; 12: 294-300.

[135] Zhang Y, Ng HH, Erdjument-Bromage H, Tempst P, Bird A and Reinberg D. Analysis of the NuRD subunits reveals a histone deacetylase core complex and a connection with DNA methylation. Genes Dev 1999; 13: 1924-1935.

[136] Xue Y, Wong J, Moreno GT, Young MK, Cote J and Wang W. NURD, a novel complex with both ATP-dependent chromatin-remodeling and histone deacetylase activities. Mol Cell 1998; 2: 851-861.

[137] Shi YJ, Matson C, Lan F, Iwase S, Baba T and Shi Y. Regulation of LSD1 histone demethylase activity by its associated factors. Mol Cell 2005; 19: 857-864.

[138] Humphrey GW, Wang Y, Russanova VR, Hirai T, Qin J, Nakatani Y and Howard BH. Stable histone deacetylase complexes distinguished by the presence of SANT domain proteins CoREST/kiaa0071 and Mta-L1. J Biol Chem 2001; 276: 6817-6824.

[139] Guenther MG, Yu J, Kao GD, Yen TJ and Lazar MA. Assembly of the SMRT-histone deacetylase 3 repression complex requires the TCP-1 ring complex. Genes Dev 2002; 16: 3130-3135.

[140] Yang WM, Tsai SC, Wen YD, Fejer G and Seto E. Functional domains of histone deacetylase-3. J Biol Chem 2002; 277: 9447-9454.

[141] Godman CA, Joshi R, Tierney BR, Greenspan E, Rasmussen TP, Wang HW, Shin DG, Rosenberg DW and Giardina C. HDAC3 impacts multiple oncogenic pathways in colon cancer cells with effects on Wnt and vitamin D signaling. Cancer Biol Ther 2008; 7: 1570-1580.

[142] Spurling CC, Godman CA, Noonan EJ, Rasmussen TP, Rosenberg DW and Giardina C. HDAC3 overexpression and colon cancer cell proliferation and differentiation. Mol Carcinog 2008; 47: 137-147.

[143] Weichert W, Roske A, Gekeler V, Beckers T, Stephan C, Jung K, Fritzsche FR, Niesporek S, Denkert C, Dietel M and Kristiansen G. Histone deacetylases 1, 2 and 3 are highly expressed in prostate cancer and HDAC2 expression is associated with shorter PSA relapse time after radical prostatectomy. Br J Cancer 2008; 98: 604-610.

[144] Giannini R and Cavallini A. Expression analysis of a subset of coregulators and three nuclear receptors in human colorectal carcinoma. Anticancer Res 2005; 25: 4287-4292.
[145] Chen JS, Faller DV and Spanjaard RA. Short-chain fatty acid inhibitors of histone deacetylases: promising anticancer therapeutics? Curr Cancer Drug Targets 2003; 3: 219-236.
[146] Nakagawa M, Oda Y, Eguchi T, Aishima S, Yao T, Hosoi F, Basaki Y, Ono M, Kuwano M, Tanaka M and Tsuneyoshi M. Expression profile of class I histone deacetylases in human cancer tissues. Oncol Rep 2007; 18: 769-774.
[147] Bartling B, Hofmann HS, Boettger T, Hansen G, Burdach S, Silber RE and Simm A. Comparative application of antibody and gene array for expression profiling in human squamous cell lung carcinoma. Lung Cancer 2005; 49: 145-154.
[148] Krusche CA, Wulfing P, Kersting C, Vloet A, Bocker W, Kiesel L, Beier HM and Alfer J. Histone deacetylase-1 and -3 protein expression in human breast cancer: a tissue microarray analysis. Breast Cancer Res Treat 2005; 90: 15-23.
[149] Wang J, Saunthararajah Y, Redner RL and Liu JM. Inhibitors of histone deacetylase relieve ETO-mediated repression and induce differentiation of AML1-ETO leukemia cells. Cancer Res 1999; 59: 2766-2769.
[150] Wilson AJ, Byun DS, Popova N, Murray LB, L'Italien K, Sowa Y, Arango D, Velcich A, Augenlicht LH and Mariadason JM. Histone deacetylase 3 (HDAC3) and other class I HDACs regulate colon cell maturation and p21 expression and are deregulated in human colon cancer. J Biol Chem 2006; 281: 13548-13558.
[151] de Ruijter AJ, van Gennip AH, Caron HN, Kemp S and van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J 2003; 370: 737-749.
[152] Wolffe AP. Histone deacetylase: a regulator of transcription. Science 1996; 272: 371-372.
[153] Schneider G, Reichert M, Saur D, Hamacher R, Fritsch R and Schmid RM. HDAC3 is linked to cell cycle machinery in MiaPaCa2 cells by regulating transcription of skp2. Cell Prolif 2007; 40: 522-531.
[154] Li Y, Kao GD, Garcia BA, Shabanowitz J, Hunt DF, Qin J, Phelan C and Lazar MA. A novel histone deacetylase pathway regulates mitosis by modulating Aurora B kinase activity. Genes Dev 2006; 20: 2566-2579.
[155] Ishii S, Kurasawa Y, Wong J and Yu-Lee LY. Histone deacetylase 3 localizes to the mitotic spindle and is required for kinetochore-microtubule attachment. Proc Natl Acad Sci U S A 2008; 105: 4179-4184.
[156] Bhaskara S, Knutson SK, Jiang G, Chandrasekharan MB, Wilson AJ, Zheng S, Yenamandra A, Locke K, Yuan JL, Bonine-Summers AR, Wells CE, Kaiser JF, Washington MK, Zhao Z, Wagner FF, Sun ZW, Xia F, Holson EB, Khabele D and Hiebert SW. Hdac3 is essential for the maintenance of chromatin structure and genome stability. Cancer Cell 2010; 18: 436-447.
[157] Jin JS, Tsao TY, Sun PC, Yu CP and Tzao C. SAHA Inhibits the Growth of Colon Tumors by Decreasing Histone Deacetylase and the Expression of Cyclin D1 and Survivin. Pathol Oncol Res 2012; 18: 713-20.
[158] Mariadason JM. Dissecting HDAC3-mediated tumor progression. Cancer Biol Ther 2008; 7: 1581-1583.
[159] Takami Y and Nakayama T. N-terminal region, C-terminal region, nuclear export signal, and deacetylation activity of histone deacetylase-3 are essential for the viability of the DT40 chicken B cell line. J Biol Chem 2000; 275: 16191-16201.
[160] Wu MZ, Tsai YP, Yang MH, Huang CH, Chang SY, Chang CC, Teng SC and Wu KJ. Interplay between HDAC3 and WDR5 is essential for hypoxia-induced epithelial-mesenchymal transition. Mol Cell 2011; 43: 811-822.
[161] Knutson SK, Chyla BJ, Amann JM, Bhaskara S, Huppert SS and Hiebert SW. Liver-specific deletion of histone deacetylase 3 disrupts metabolic transcriptional networks. EMBO J 2008; 27: 1017-1028.
[162] Balasubramanian S, Verner E and Buggy JJ. Isoform-specific histone deacetylase inhibitors: the next step? Cancer Lett 2009; 280: 211-221.
[163] Thaler F and Minucci S. Next generation histone deacetylase inhibitors: the answer to the search for optimized epigenetic therapies? Expert Opin Drug Discov 2011; 6: 393-404.
[164] Witt O, Deubzer HE, Milde T and Oehme I. HDAC family: What are the cancer relevant targets? Cancer Lett 2009; 277: 8-21.
[165] McKinsey TA. Isoform-selective HDAC inhibitors: closing in on translational medicine for the heart. J Mol Cell Cardiol 2011; 51: 491-496.
[166] Bieliauskas AV and Pflum MK. Isoform-selective histone deacetylase inhibitors. Chem Soc Rev 2008; 37: 1402-1413.
[167] Rasheed WK, Johnstone RW and Prince HM. Histone deacetylase inhibitors in cancer therapy. Expert Opin Investig Drugs 2007; 16: 659-678.
[168] Garber K. HDAC inhibitors overcome first hurdle. Nat Biotechnol 2007; 25: 17-19.
[169] Wells CE, Bhaskara S, Stengel KR, Zhao Y, Sirbu B, Chagot B, Cortez D, Khabele D, Chazin

WJ, Cooper A, Jacques V, Rusche J, Eischen CM, McGirt LY and Hiebert SW. Inhibition of histone deacetylase 3 causes replication stress in cutaneous T cell lymphoma. PLoS One 2013; 8: e68915.
[170] Malvaez M, McQuown SC, Rogge GA, Astarabadi M, Jacques V, Carreiro S, Rusche JR and Wood MA. HDAC3-selective inhibitor enhances extinction of cocaine-seeking behavior in a persistent manner. Proc Natl Acad Sci U S A 2013; 110: 2647-2652.
[171] Guenther MG, Barak O and Lazar MA. The SMRT and N-CoR corepressors are activating cofactors for histone deacetylase 3. Mol Cell Biol 2001; 21: 6091-6101.
[172] You SH, Lim HW, Sun Z, Broache M, Won KJ and Lazar MA. Nuclear receptor co-repressors are required for the histone-deacetylase activity of HDAC3 in vivo. Nat Struct Mol Biol 2013; 20: 182-187.
[173] Bhaskara S, Chyla BJ, Amann JM, Knutson SK, Cortez D, Sun ZW and Hiebert SW. Deletion of histone deacetylase 3 reveals critical roles in S phase progression and DNA damage control. Mol Cell 2008; 30: 61-72.
[174] Sun Z, Feng D, Fang B, Mullican SE, You SH, Lim HW, Everett LJ, Nabel CS, Li Y, Selvakumaran V, Won KJ and Lazar MA. Deacetylase-independent function of HDAC3 in transcription and metabolism requires nuclear receptor corepressor. Mol Cell 2013; 52: 769-782.
[175] Guo C, Gow CH, Li Y, Gardner A, Khan S and Zhang J. Regulated clearance of histone deacetylase 3 protects independent formation of nuclear receptor corepressor complexes. J Biol Chem 2012; 287: 12111-12120.
[176] Zhang X, Ozawa Y, Lee H, Wen YD, Tan TH, Wadzinski BE and Seto E. Histone deacetylase 3 (HDAC3) activity is regulated by interaction with protein serine/threonine phosphatase 4. Genes Dev 2005; 19: 827-839.
[177] Watson PJ, Fairall L, Santos GM and Schwabe JW. Structure of HDAC3 bound to co-repressor and inositol tetraphosphate. Nature 2012; 481: 335-340.
[178] Bassi MT, Ramesar RS, Caciotti B, Winship IM, De Grandi A, Riboni M, Townes PL, Beighton P, Ballabio A, Borsani G. X-linked late-onset sensorineural deafness caused by a deletion involving OA1 and a novel gene containing WD-40 repeats. Am J Hum Genet 1999; 64: 1604-1616.
[179] Dong X, Tsuda L, Zavitz KH, Lin M, Li S, Carthew RW, Zipursky SL. ebi regulates epidermal growth factor receptor signaling pathways in Drosophila. Genes Dev 1999; 13: 954-965.
[180] Zhang X, Dormady SP and Basch RS. Identification of four human cDNAs that are differentially expressed by early hematopoietic progenitors. Exp Hematol 2000; 28: 1286-1296.
[181] Perissi V, Scafoglio C, Zhang J, Ohgi KA, Rose DW, Glass CK, Rosenfeld MG. TBL1 and TBLR1 phosphorylation on regulated gene promoters overcomes dual CtBP and NCoR/SMRT transcriptional repression checkpoints. Mol Cell 2008; 29: 755-766.
[182] Perissi V, Aggarwal A, Glass CK, Rose DW and Rosenfeld MG. A corepressor/coactivator exchange complex required for transcriptional activation by nuclear receptors and other regulated transcription factors. Cell 2004; 116: 511-526.
[183] Choi HK, Choi KC, Yoo JY, Song M, Ko SJ, Kim CH, Ahn JH, Chun KH, Yook JI and Yoon HG. Reversible SUMOylation of TBL1-TBLR1 regulates β-catenin-mediated Wnt signaling. Mol Cell 2011; 43: 203-216.
[184] Daniels G, Li Y, Gellert LL, Zhou A, Melamed J, Wu X, Zhang X, Zhang D, Meruelo D, Logan SK, Basch R and Lee P. TBLR1 as an androgen receptor (AR) coactivator selectively activates AR target genes to inhibit prostate cancer growth. Endocr Relat Cancer 2014; 21: 127-142.
[185] Spain BH, Bowdish KS, Pacal AR, Staub SF, Koo D, Chang CY, Xie W and Colicelli J. Two human cDNAs, including a homolog of Arabidopsis FUS6 (COP11), suppress G-protein- and mitogen-activated protein kinase-mediated signal transduction in yeast and mammalian cells. Mol Cell Biol 1996; 16: 6698-6706.
[186] Jin DY, Teramoto H, Giam CZ, Chun RF, Gutkind JS and Jeang KT. A human suppressor of c-Jun N-terminal kinase 1 activation by tumor necrosis factor alpha. J Biol Chem 1997; 272: 25816-25823.
[187] Peng YC, Breiding DE, Sverdrup F, Richard J and Androphy EJ. AMF-1/Gps2 binds p300 and enhances its interaction with papillomavirus E2 proteins. J Virol 2000; 74: 5872-5879.
[188] Cardamone MD, Krones A, Tanasa B, Taylor H, Ricci L, Ohgi KA, Glass CK, Rosenfeld MG and Perissi V. A protective strategy against hyperinflammatory responses requiring the nontranscriptional actions of GPS2. Mol Cell 2012; 46: 91-104.
[189] Jakobsson T, Venteclef N, Toresson G, Damdimopoulos AE, Ehrlund A, Lou X, Sanyal S, Steffensen KR, Gustafsson JA and Treuter E. GPS2 is required for cholesterol efflux by triggering histone demethylation, LXR recruitment, and coregulator assembly at the ABCG1 locus. Mol Cell 2009; 34: 510-518.
[190] Peng YC, Kuo F, Breiding DE, Wang YF, Mansur CP and Androphy EJ. AMF1 (GPS2) modulates p53 transactivation. Mol Cell Biol 2001; 21: 5913-5924.
[191] Sanyal S, Bavner A, Haroniti A, Nilsson LM, Lundasen T, Rehnmark S, Witt MR, Einarsson C, Talianidis I, Gustafsson JA and Treuter E.

Involvement of corepressor complex subunit GPS2 in transcriptional pathways governing human bile acid biosynthesis. Proc Natl Acad Sci U S A 2007; 104: 15665-15670.

[192] Venteclef N, Jakobsson T, Ehrlund A, Damdimopoulos A, Mikkonen L, Ellis E, Nilsson LM, Parini P, Janne OA, Gustafsson JA, Steffensen KR and Treuter E. GPS2-dependent corepressor/SUMO pathways govern anti-inflammatory actions of LRH-1 and LXRbeta in the hepatic acute phase response. Genes Dev 2010; 24: 381-395.

[193] Zhang D, Harry GJ, Blackshear PJ and Zeldin DC. G-protein pathway suppressor 2 (GPS2) interacts with the regulatory factor X4 variant 3 (RFX4_v3) and functions as a transcriptional co-activator. J Biol Chem 2008; 283: 8580-8590.

[194] Cheng X and Kao HY. G protein pathway suppressor 2 (GPS2) is a transcriptional corepressor important for estrogen receptor alpha-mediated transcriptional regulation. J Biol Chem 2009; 284: 36395-36404.

[195] Cardamone MD, Tanasa B, Chan M, Cederquist CT, Andricovich J, Rosenfeld MG and Perissi V. GPS2/KDM4A Pioneering Activity Regulates Promoter-Specific Recruitment of PPARgamma. Cell Rep 2014; 8: 163-176.

[196] Toubal A, Clement K, Fan R, Ancel P, Pelloux V, Rouault C, Veyrie N, Hartemann A, Treuter E and Venteclef N. SMRT-GPS2 corepressor pathway dysregulation coincides with obesity-linked adipocyte inflammation. J Clin Invest 2013; 123: 362-379.

[197] Bi H, Li S, Wang M, Jia Z, Chang AK, Pang P, Wu H. SUMOylation of GPS2 protein regulates its transcription-suppressing function. Mol Biol Cell 2014; 25: 2499-508

[198] Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Auclair D, Bochicchio J, Carneiro MO, Carter SL, Cibulskis K, Erlich RL, Greulich H, Lawrence MS, Lennon NJ, McKenna A, Meldrim J, Ramos AH, Ross MG, Russ C, Shefler E, Sivachenko A, Sogoloff B, Stojanov P, Tamayo P, Mesirov JP, Amani V, Teider N, Sengupta S, Francois JP, Northcott PA, Taylor MD, Yu F, Crabtree GR, Kautzman AG, Gabriel SB, Getz G, Jager N, Jones DT, Lichter P, Pfister SM, Roberts TM, Meyerson M, Pomeroy SL and Cho YJ. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. Nature 2012; 488: 106-110.

[199] Bien-Willner GA and Mitra RD. Mutation and expression analysis in medulloblastoma yields prognostic variants and a putative mechanism of disease for i17q tumors. Acta Neuropathol Commun 2014; 2: 74.

[200] O'Meara E, Stack D, Phelan S, McDonagh N, Kelly L, Sciot R, Debiec-Rychter M, Morris T, Cochrane D, Sorensen P and O'Sullivan MJ. Identification of an MLL4-GPS2 fusion as an oncogenic driver of undifferentiated spindle cell sarcoma in a child. Genes Chromosomes Cancer 2014; [Epub ahead of print].

[201] Cho YW, Hong T, Hong S, Guo H, Yu H, Kim D, Guszczynski T, Dressler GR, Copeland TD, Kalkum M and Ge K. PTIP associates with MLL3- and MLL4-containing histone H3 lysine 4 methyltransferase complex. J Biol Chem 2007; 282: 20395-20406.

[202] McPherson A, Wu C, Hajirasouliha I, Hormozdiari F, Hach F, Lapuk A, Volik S, Shah S, Collins C and Sahinalp SC. Comrad: detection of expressed rearrangements by integrated analysis of RNA-Seq and low coverage genome sequence data. Bioinformatics 2011; 27: 1481-1488.

[203] Frattini V, Trifonov V, Chan JM, Castano A, Lia M, Abate F, Keir ST, Ji AX, Zoppoli P, Niola F, Danussi C, Dolgalev I, Porrati P, Pellegatta S, Heguy A, Gupta G, Pisapia DJ, Canoll P, Bruce JN, McLendon RE, Yan H, Aldape K, Finocchiaro G, Mikkelsen T, Prive GG, Bigner DD, Lasorella A, Rabadan R and Iavarone A. The integrated landscape of driver genomic alterations in glioblastoma. Nat Genet 2013; 45: 1141-1149.