Nuclear receptor coregulators as a new paradigm for therapeutic targeting

Elaine Y. Hsia[a,c], **Michael L. Goodson**[d], **June X. Zou**[b], **Martin L. Privalsky**[d], and **Hong-Wu Chen**[a,c,e]

[a]Department of Biochemistry and Molecular Medicine, University of California at Davis, Sacramento, CA95817, USA

[b]Department of Internal Medicine, School of Medicine, University of California at Davis, Sacramento, CA95817, USA

[c]UC Davis Cancer Center/Basic Sciences, University of California at Davis, Sacramento, CA95817, USA

[d]Department of Microbiology, College of Biological Sciences, University of California at Davis, Davis, CA95616, USA

Abstract

The complex function and regulation of nuclear receptors cannot be fully understood without a thorough knowledge of the receptor-associated coregulators that either enhance (coactivators) or inhibit (corepressors) transcription. While nuclear receptors themselves have garnered much attention as therapeutic targets, the clinical and etiological relevance of the coregulators to human diseases is increasingly recognized. Aberrant expression or function of coactivators and corepressors has been associated with malignant and metabolic disease development. Many of them are key epigenetic regulators and utilize enzymatic activities to modify chromatin through histone acetylation/deacetylation, histone methylation/demethylation or chromatin remodeling. In this review, we showcase and evaluate coregulators with the most promising therapeutic potential based on their physiological roles and involvement in various diseases that are revealed thus far. We also describe the structural features of the coactivator and corepressor functional domains and highlight areas that can be further explored for molecular targeting.

Keywords

p160/SRC; PGC-1; ANCCA; SMRT; NCoR; histone methylation; histone acetylation; cancer; diabetes; obesity

[e]Corresponding author hwzchen@ucdavis.edu Phone: (916)-734-7743, Fax: (916)-734-0190.

1. Introduction

The significance of understanding transcriptional regulation by the nuclear hormone receptors (NRs) is underscored by the diverse diseases, such as cancer, where numerous aberrations in hormone signaling pathways are uncovered. Transcriptional regulation by NRs involves ordered and dynamic protein-protein interactions between the receptor, associated coregulators, and the RNA polymerase II transcriptional machinery at the chromatin of target genes. Many coregulators possess enzymatic activities or recruit multi-subunit enzymatic protein complexes to mediate specific chromatin modifications that result in either activate or repress transcription (see below).

Coregulators can be divided into two general classes, namely, coactivators and corepressors. Coactivators are generally characterized by their ability to enhance NR transactivation by interacting with the N-terminus and/or the C-terminal ligand binding domain (LBD) domain of agonist-bound NRs. The counterparts of coactivators, called corepressors, were identified as mediators for selectively repressing NR-dependent gene transcription through interaction with unliganded or antagonist-bound (or in some cases, agonist-bound) NRs on their target genes [1].

Because many coregulators influence the activity of multiple nuclear hormone receptors and thus the transcriptional output of many gene networks, it is not surprising that disruption of their normal function or expression can contribute to a vast spectrum of physiological abnormalities and diseases. Many studies using mouse models support this notion and have contributed to our understanding of coregulators for normal biological function. For example, gene knockout studies have demonstrated important roles for individual members of the p160 family of coactivators (see below) in hormonal responses and organ developments during reproduction, metabolism, and growth [2]. Furthermore, the phenotypic defects were not restricted to hormone-regulated tissues and processes, reflecting in some circumstances a more general role played by the coregulators in control of gene expression. While we acknowledge that many coregulators associate with and mediate the functions of NRs besides steroid receptors, their aberrant expression and function appear to be best understood so far in the steroid hormone responsive human malignancies such as breast cancer and prostate cancer (e.g. the p160/SRC family) or metabolism and energy homeostasis (e.g. PGC-1). Here, we outline the structure and function of coregulators that can thus be considered as highly attractive and promising, new therapeutic targets.

2. Coactivators – Structure, function and therapeutic implications

Enzymatic modification of chromatin structure is at the heart of gene regulation at the transcriptional level. Coactivators can promote gene-specific NR-mediated transcription via several activities. Changes in post-translational modifications on core histone tails – particularly acetylation and methylation – serve as a crucial step in the remodeling of chromatin structure during gene expression. Loss-of-function experiments revealed that the histone acetylase (HAT) activities of the general coactivator CBP and its associated factor p/CAF are important for enhancing NR transactivation [3]. However, transactivation *in vivo* requires their indirect association with NRs through the p160 coactivators. The intrinsic

HAT activity of p160 coactivators in some cases may not be essential for NR-dependent transactivation and, as such, the p160 proteins may primarily serve as adaptors for recruiting HAT containing coactivator complexes in a promoter- and NR-specific context [3].

Other notable classes of histone modifying coactivators that enhance transactivation of NRs include methyltransferases (CARM1 and PRMT1) and demethylases (LSD1, JMJD2a, JMJD2c). Like CBP and p/CAF, CARM1 acts as a secondary coactivator through interaction with the 160 family. SWI/SNF/BRG complexes interact directly with NRs and utilize the energy of ATP hydrolysis to remodel local chromatin structure a key step for transcription [1]. The histone modifying, chromatin remodeling, and RNAPII activating mediator (DRIP/TRAP) coactivator complexes, with their different mechanisms of action, may work in concert to facilitate and enhance NR mediated gene transcription [4].

2.1. The p160/SRC family – key mediators of NR function

2.1.1. The structural determinants for p160/SRC interaction with the NRs—The p160/SRC genes were among the first gene families characterized as coactivators for NRs and include SRC-1, TIF2/GRIP-1, and ACTR/AIB1/RAC3/SRC-3/TRAM-1. The p160s serve as a platform for the assembly of coactivator complexes on the regulatory regions of genes that are targeted by ligand-bound NRs. They thus act as bridging factors between the receptor and other coregulators such as HAT proteins p300/CBP and p/CAF and the mediator complex. Proteins encoded by the p160s family possess conserved homologous domains – consisting of 50-55% sequence similarity - that confer these common functions.

The central receptor interaction domain (RID) of the p160s contains three LXXLL motifs that form amphipathic alpha-helices that are responsible for direct association with the LBD of NRs. The structural determinants of interaction and binding affinity can vary for each p160, depending on the receptor. On the receptor side, the interaction usually requires a ligand-dependent formation of a hydrophobic cleft in the LBD and sometimes the participation of AF-1 and AF-2 [5-6]. On the coactivator side, the interaction requires at least one LXXLL motif. Receptor-specific or preferential utilization of LXXLL motifs dependent, in part, on amino acid sequences adjacent to the motis [2, 7-8]. Although they do not bind DNA directly, the p160s contain two intrinsic transcriptional activation domains (AD1 and AD2) in the C-terminal region [2]. Interestingly, AD1 contains three LXXLL motifs and is responsible for interaction with CBP/p300 and p/CAF. AD2, on the other hand, interacts with CARM1 and PRMT1 and partly confers the HAT activity of SRC-1 and ACTR. Intriguingly, the HAT domain of ACTR shares several sequence motifs with that of CLOCK, a key circadian regulator and a HAT, including a glutamine-rich (Q-rich) feature [9].

The molecular determinants of p160 interaction with estrogen receptor-α (ERα) have been intensively investigated in the context of ligand specificity and therapeutic modulation. It should be noted that the overall structural folding of the LBD is highly conserved among NRs, and that ligand binding induces similar conformational changes [10-11]. The LBD comprises twelve alpha-helices and two beta-sheets that form a hydrophobic binding pocket for ligands. Helices 3, 4, 5, and 12 together form a hydrophobic groove that interacts with the LXXLL amphipathic alpha-helix of the RID in p160s when agonist such as estradiol or

diethylstilbestrol is bound [5]. The positioning of helix 12 as part of the hydrophobic groove, in particular, has been revealed to be critical for formation of the coactivator binding surface. Structural studies show that ERα undergoes a different conformational change in the AF-2, which lies within the LBD and contains helix 12, depending on whether it binds agonists, antagonists or other selective ER modulators (SERMs). Binding by 4-hydroxy-tamoxifen or raloxifene renders helix 12 positioning in a way that prevents association with coactivators and instead favors association with corepressors.

Aside from ligand specificity, the context of receptor target gene regulatory region to which a NR binds, particularly the sequence of the hormone response elements, may also modulate receptor conformation and affinity for specific coregulators. This concept has been demonstrated in vitro using ERα and EREs from various estrogen target genes [12-13]. Thus, at least three factors – namely ligand, DNA sequence, and presence of coactivators and corepressors – likely influence the transcriptional activation status of NRs and their recruitment of coregulator complexes in a promoter and cell type-specific manner.

2.1.2. The p160/SRC family involvement in cancer—The aberrant expression of p160 family members in various cancers - as well as their roles and functions in tumorigenesis and disease progression – is an ongoing area of intense research. Gene amplification and/or overexpression of SRC-1, TIF2 and ACTR/AIB1 have been independently reported in clinical samples from breast, prostate and ovarian cancer patients (summarized in reference 14). These findings are not restricted to hormone-responsive malignancies, however, which again reflects the actions of p160s in a diverse range of tissues [14] . Significant clinicopathological correlations were observed for overexpression with high grade, advanced disease stage, and lower disease-free survival for subsets of the cancer patients. In some cohorts of breast and prostate cancers, high SRC-1, TIF2 and ACTR/AIB1 expression have been linked to greater disease recurrence after hormone deprivation therapies [15-23]. Notably, elevated co-expression of ACTR/AIB1 with members of the HER/ErbB family (HER1, HER2, or HER3) was associated with poor response to tamoxifen therapy in invasive breast tumors [19], while coexpression with ER was associated with improved response [24-25].

While clinical studies highlight the potential value of p160s as prognostic indicators, studies using mouse and tissue culture models have revealed their tumor-promoting functions and their roles in disease progression, including disease recurrence after hormone depletion in breast and prostate cancer ([14] and references therein). Overexpression of ACTR/AIB1 or RNAi-mediated depletion of p160 coactivators has demonstrated that their expression is critical for the proliferation of hormone-dependent and –independent breast and prostate cancer cells and tamoxifen resistance [22, 26-29]. In addition to the classical ligand-mediated pathway, ER and androgen receptor (AR) can be activated to increase expression of cell proliferation genes through growth factor/kinase mediated signaling pathways that elicit phosphorylation of the receptors and their coactivators. Whether this non-classical pathway is critically involved in hormone independence and resistance to hormone blockade therapies is still being investigated.

MAPK phosphorylation of SRC-1 and TIF2 at specific residues, for example, is required for optimal androgen-independent activation of AR by IL-6 and EGF [30-32]. Schiff et al reported that HER2/Neu phosphorylation and/or activation of downstream kinases is required for ACTR recruitment to the promoters of ER target genes and to enhance the ER agonist activity of tamoxifen in a resistant clone of MCF-7 breast cancer cells [33]. However, subsequent in vivo study suggests that non-genomic activation of EGFR/HER2 by ER is the predominant mechanism of acquired tamoxifen resistance and that ER target genes continue to be repressed despite agonistic effect on tumor growth [34]. More recent studies showed that RNAi-mediated disruption of ACTR inhibits agonist properties of tamoxifen [35] as well as EGF-induced proliferation in tamoxifen resistant ER positive breast cancer cell lines that express high levels of ACTR and HER1/HER2 [36], supporting a crucial role for this coactivator in acquired tamoxifen resistance [27].

2.1.3. Therapeutic modulation of ER signaling through altered coregulator interaction – a model for targeting NR function—The preclinical and clinical studies above attest to the important contribution of p160 coactivators in ER-positive breast cancer cell proliferation through receptor signaling, a concept that is further supported by anti-estrogen actions on ER-coregulator interactions *in vitro* (see section 2.1.1). However, SERMs such as tamoxifen and raloxifene display partial agonist or antagonist activity *in vivo* depending on tissue type likely involving selective recruitment of coactivator or corepressor complexes to target genes [37]. Such swing of effect is believed to be influenced by the relative contribution of coactivators and corepressors that are expressed in different tissues. For example, high levels of SRC-1 in endometrial cancer cells may mediate the agonist activity of tamoxifen in this specific cell type [38].

While AF-1 contributes to tissue-selective activation by SERMs, the positioning of helix 12 induced by SERMs to the LBD hydrophobic groove is believed to influence the affinity of the receptor for the coregulators and to depend on the specific SERM ligand. In the case of tamoxifen, helix 12 is positioned in a way that mimics the interaction of coactivator LXXLL-containing peptide with the LBD [39]. This and other work suggests that helix 12 actually competes with corepressor for binding in the presence of SERM agonist, while removal of helix 12 from the hydrophobic cleft in the presence of a full antagonist such as ICI182,780 promotes corepressor binding [37].

While all known SERMs and ER antagonists function by binding to the ER LBD, the identification of coactivator binding inhibitors has emerged as an alternative approach to effectively inhibit estrogen action. The bulk of this work has relied heavily on chemical and cell based screening of small molecules that contain substituents mimicking the structure of coactivator LXXLL alpha-helical consensus sequence, and that directly compete with the coactivator for high affinity (at low micromolar range) binding to the coactivator binding groove in the ER LBD [40-47]. Given that the inhibitors do not significantly affect receptor ligand binding, it is possible that these new peptide inhibitors or functionally equivalent small molecule compounds could be developed for use in conjunction with first-line antagonists such as tamoxifen to prevent or treat hormone refractory breast cancer in susceptible patients. In support of this idea, studies suggest that disruption of ER interactions with coactivator proteins can inhibit cell growth of endocrine-resistant breast cancer [48-49].

Importantly, it has been shown that analogous structural mimetic strategies can be applied to target other NRs including androgen receptor and thyroid hormone receptor [50-51].

2.2. PGC-1α – a tissue-specific coactivator for metabolic regulation and energy homeostasis

2.2.1. Physiological roles and involvement in metabolic diseases—PGC-1α represents an example in which a primary regulation of transcriptional programs by NRs is at the level of a transcriptional coactivator. PGC-1α is one of three members of the PGC-1 gene family that possess highly homologous functional domains including a transcriptional activation domain with NR interacting LXXLL motifs in the N-terminus and an RNA-binding motif in the C-terminus. Although they have not been demonstrated to possess any enzymatic activity, full transcriptional activation by PGC-1 likely depends on recruitment of several classes of coactivators, including Mediator, SWI/SNF complex and p160/SRC members, through distinct interaction domains at the PGC-1 [52-54]. While PGC-1α shares some common functions with the PGC-1β isoform, such as regulating mitochondrial biogenesis, energy metabolism and fatty acid oxidation, PGC-1α is unique in that its expression is upregulated by cold, fasting and exercise, and in that it stimulates adaptive thermogenesis, heme biosynthesis and liver gluconeogenesis [55].

The diverse, tissue-specific metabolic functions of PGC-1α are believed to be mediated through coactivation of particular transcription factors that regulate gluconeogenic and mitochondrial genes in response to environmental stimuli. For example, UCP-1, a mitochondrial gene expressed specifically in brown adipocytes that is critical for activating cold-induced thermogenesis, is induced through PGC-1α coactivation of PPAR-γ and TR [56]. By uncoupling oxidative phosphorylation through the mitochondrial respiratory chain, UCP-1 contributes to the generation of heat through brown adipose tissue. By coactivating PPAR-α and ERR-α, PGC-1α regulates several genes involved in mitochondrial biogenesis, respiration and fatty acid oxidation in cardiac and skeletal muscle [57-58], which likely explains its important role in maintaining normal oxidative capacity and energy metabolism in these tissues [59-61]. PGC-1α also enhances transcriptional activity of glucocorticoid receptor and hepatocyte nuclear factor-4α, two NRs that regulate expression of key gluconeogenic genes in liver [62]. It is believed that the two separate metabolic pathways of gluconeogenesis and fatty acid oxidation, integrated through PGC-1α, function to maintain energy and nutrient homeostasis during fasting [55].

In agreement with its role as a coordinator of diverse metabolic processes, altered PGC-1 expression levels in various tissues have been implicated in diseases that involve impaired mitochondrial function, including type 2 diabetes (T2D). In skeletal muscle, a key site for insulin action in vivo, PGC-1α induces expression of the insulin-sensitive glucose transporter GLUT4 and enhances glucose uptake through coactivation of the muscle-selective transcription factor MEF2C [63]. Reduced PGC-1α expression in skeletal muscle or adipose tissue was reportedly associated with T2D patients or with morbidly obese and insulin resistant subjects, respectively [64-66]. The finding that genes involved in oxidative phosphorylation are also downregulated in T2D patients [64, 67] supports the hypothesis that PGC-1α and mitochondrial dysfunction constitute a cellular mechanism for insulin

resistance and T2D pathology. In several murine models of insulin-deficiency or insulin-resistance, hepatic PGC-1α mRNA was dramatically elevated [62]. Liver-specific expression of PGC-1α transgene increased blood glucose and insulin levels in normal non-fasting animals [62], while PGC-1 deficiency in the liver enhanced insulin sensitivity [68]. Thus, both increased and decreased PGC-1α expression in different metabolic tissues may contribute to the metabolic disturbances characteristic of T2D. Furthermore, animal models suggest that decreased PGC-1α in the heart and brain may promote cardiac hypertrophy and failure, and neurodegenerative diseases, two conditions that are accompanied by critical defects in metabolism [69].

2.2.2 PGC-1α regulators as potential therapeutic targets—As an integrator of diverse metabolic processes that influence health and disease, PGC-1α poses as an attractive target for the prevention and treatment of metabolic disorders. The aforementioned pre-clinical and clinical studies imply that modulation of PGC-1α activity could impact mitochondrial function in T2D subjects. Much of the evidence that supports this prospect has focused on SIRT-1, an NAD(+)-dependent histone deacetylase of the sirtuin family, that enhances PGC-1α activity through deacetylation of multiple lysine residues in response to cellular nutrient signals [70]. Elevated pyruvate and NAD+ increase SIRT-1 protein levels and activity in the fasting liver where it is required for PGC-1α upregulation of gluconeogenic genes to increase glucose output. Subsequently, modulation of SIRT-1 activity was found to impact mitochondrial function and whole-body metabolism. Enhancing SIRT-1 activity through supplementation of the polyphenol resveratrol increased mitochondrial biogenesis, muscle function, and insulin sensitivity through PGC-1α transcriptional programs in mouse models of diet-induced obesity [71-72]. Increased oxidative capacity in skeletal muscle and improved glucose and lipid metabolism in the liver were also observed in these studies. However, more recent work in vitro suggests that resveratrol's effects are not mediated through direct activation of SIRT-1 [73].

Whether indirect activation of PGC-1α through resveratrol or other small molecules with similar activity presents a valid approach to treat T2D is still an active area of investigation. More recent studies have established that resveratrol reverses hyperglycemia in a diabetic rat model. This observation was accompanied by positive physiological changes including improved plasma insulin levels and liver glycogen content, with the latter effect associated with modulation of enzymatic activities that control gluconeogenesis [74-75]. These findings, together with the overall improvement in glucose homeostasis seen in mice, suggest that resveratrol may not promote PGC-1α enhancement of liver gluconeogenesis, a property that would be highly desirable as an effective treatment for T2D. Furthermore, the enhancement of insulin sensitivity in muscle through resveratrol supports the hypothesis that induction of PGC-1α activity can be translated to positive therapeutic outcomes for diabetic patients. Since mitochondrial dysfunction has been linked to other diseases such as cardiomyopathy and neurodegeneration, therapeutic targeting of PGC-1α may extend beyond diabetes.

2.3. Coactivators with histone and chromatin modifying activities

Mounting evidence suggests that dynamic multi-level changes in chromatin structure that are mediated by transcriptional coregulators strongly impact cellular processes including differentiation, cell death, inflammation, and oncogenesis [76-79]. Consequently, epigenetic aberrations in gene expression attributed to deregulated coregulators may play important roles in various human diseases. This notion is underscored by the observation, for example, that many histone demethylases are inactivated or overexpressed in various human malignancies [80]. Furthermore, inhibitors of DNA methyltransferases and histone deacetylases are currently touted as potential therapeutic compounds for their ability to derepress epigenetically silenced tumor suppressor genes (see section 3.3). Here, we will highlight recently identified coactivators, some of which have been linked to cancer, that directly interact with and/or mediate chromatin histone modifications to drive hormone-responsive or -independent gene expression.

2.3.1. Histone demethylases – important mediators in AR-dependent gene transcription

LSD1: As a member of the amine oxidase family of histone demethylases, lysine-specific histone demethylase 1 (LSD1) catalyzes the cleavage of substrate alpha-carbon bond through a three-step reaction involving reduction of cofactor FAD and generation of byproducts hydrogen peroxide and formaldehyde [81-82]. The C-terminal amine oxidase-like (AOL) domain comprises the catalytic core and binds both the peptide substrate and FAD cofactor. The central Tower domain binds the corepressor CoREST which promotes stability, efficient nucleosomal association and demethylase specificity for H3K4 [83]. As methylation of H3K4 typically marks transcriptionally active genomic regions, LSD1 was initially identified and characterized as a corepressor. However, more recent studies revealed that LSD1 also targets methylated H3K9, a marker that has been found in both the promoters of silenced genes and the coding regions of actively transcribed genes [84-86]. Thus, LSD1 can act as a coactivator or corepressor depending on the chromatin context.

Association with NRs, particularly the AR, has been shown to switch the substrate specificity of LSD1 to H3K9 in vitro and in vivo. While H3K4 methylation levels were unaffected by androgen in prostate cancer cells, repressive methylation of H3K9 in the enhancer region of PSA promoter was diminished by androgen treatment of cells. LSD1 knockdown or inhibition blocked AR-dependent gene expression and H3K9 demethylation [87]. Thus, in this context, LSD1 acts as a coactivator to drive AR-mediated transcription. Similar findings have been found during ligand-stimulated transcription of ERα target genes in breast cancer cells. However, this observation was accompanied by LSD1 dependent H3K4 demethylation in the enhancer and promoter regions after loss of receptor from chromatin or under hormone starvation [88]. Collectively, these studies suggest that LSD1 is a key player in regulating hormone-responsive genes through modulation of H3 lysine methyl marks, leading to dynamic transcriptional derepression and, in the case of ER, repression in a receptor-dependent manner.

Small molecule inhibitors of LSD1 have been characterized, prompting investigation into the potential for LSD1 as a therapeutic target. These include compounds, some of which are

used to treat depression, that inhibit structurally homologous monoamine and polyamine oxidases. Identified LSD1 inhibitors have been shown to increase global H3K4 methylation in colon carcinoma and P19 embryonic carcinoma cells [89-90]. In colon cancer, this finding was accompanied by selective derepression of aberrantly silenced genes as well as decreased H3K9 methylation and increased H3K9 acetylation at the specific gene promoters [89]. Other factors may contribute to selective gene reexpression resulting from LSD1 inhibition, however, and the less well-characterized consequences of increased global H3K4 methylation suggest that further studies are required to evaluate the therapeutic efficacy and specificity of targeting LSD1 in different cell and tissue context. In addition, LSD1 knockdown derepresses hTERT expression - which is silenced in normal cells - and delays stabilization of p53 upon DNA damage [91-92]. LSD1 knockdown also represses p53 transcriptional activity by demethylating K370 on this tumor suppressor substrate [93].

An alternative strategy could employ inhibition of binding between LSD1 and specific transcription factors. Prostate cancer presents a particularly promising model to assess this targeted approach as the structural domains involved in LSD1 interaction with AR have been identified. Furthermore, LSD1 knockdown blocks androgen-dependent proliferation of prostate cancer cells [87]. High expression of LSD1 in primary prostate tumors has been correlated with high grade and disease recurrence after radical prostatectomy [94], suggesting additional involvement of LSD1 in androgen-independent receptor activation and tumor progression.

JumonjiC domain-containing proteins: Histone lysines can be mono-, di-or tri-methylated, and removal of all three forms of methylation on H3K9 is required for ligand-induced AR dependent transcription. However, the demethylation reaction catalyzed by LSD1 requires a lone pair of electrons on the substrate nitrogen, limiting its activity to mono-or dimethylated lysines and indicating the involvement of a H3K9 tri-demethylase which does not require protonated substrate nitrogen. Two separate groups identified several members of the JmjC domain-containing protein family that are capable of removing trimethyl group from H3K9 and enhancing AR-mediated transcriptional activation [95-96]. As bona fide coactivators of AR, JMJD2A, JMJD2C, and JMJD2D interact with the receptor in a ligand dependent manner. Like LSD1, JMJD2C binds PSA promoter chromatin in a ligand-independent manner where it forms a complex with ligand-activated AR and is required for H3K9 demethylation. Interestingly, JMJD2C is also associated with LSD1 on the PSA promoter, and the two coactivators can cooperatively stimulate AR-dependent transactivation [95].

The JmjC family of histone demethylases utilize a hydroxylation reaction involving Fe(II) and α-ketoglutarate as cofactors to remove substrate methyl groups, generating formaldehyde as a byproduct. As the name implies, catalytic activity is dependent on the conserved Jumonji C domain, although other functional domains not present in all members are also crucial for the demethylase activity of some JmjC proteins. The JMJD2A-C subfamily contains C-terminal PHD and Tudor domains that are involved in binding methylated histones, which are not present in the JMJD2D-F subfamily. Mutation of critical residues in the JmjC domain disrupted stimulation of AR transactivation, indicating that catalytic activity is required for the coactivation function [95-97]. Despite sequence

similarities in the JmjC domain, individual characterized demethylases have very distinct specificity with regard to both methylation site and state. Other AR coactivators belonging to the JmjC family include JHDM2A, which specifically demethylates mono- and di-methylated H3K9, and JARID1B, which removes mono-, di-, and tri-methylated forms of H3K4 [97-98]. In contrast to JMJD2C, JHDM2A recruitment to AR target gene promoters was hormone-induced, although LSD1 remained critical for optimal demethylation of H3K9 and transactivation by AR [98].

In context of their involvement in transcriptional activation of AR target genes, the aforementioned JmjC coactivators can be considered potential therapeutic targets. Knockdown of JMJD2C in LNCaP cells blocked androgen-induced cell proliferation [95], and cancer gene expression profiling analysis indicated that JMJD2C expression is upregulated in prostate cancer compared to benign prostate hyperplasia [97]. These studies suggest that the involvement of JmjC proteins in prostate cancer development and progression warrants further investigation. Furthermore, preliminary data suggest that some JmjC proteins can coactivate other NRs besides AR [95].

2.3.2. AAA+ Nuclear Coregulator Cancer-Associated (ANCCA)—We and others recently identified ANCCA, a member of the AAA+ (ATPases associated with various cellular activities) family, as a novel transcriptional coactivator for ERalpha and AR as well as c-Myc [99-101]. Members of this functionally diverse ATPase family possess conserved AAA+ ATP-binding domains and assemble into characteristic ring-shaped hexamers constituting the active ATPase holoenzyme. ATP binding sites are formed at the interface between adjacent AAA+ protein subunits. The AAA+ domain contains several structural motifs, particularly within the key SRH (second region of homology) element, believed to coordinate ATP hydrolysis and the propagation of conformational changes throughout the enzyme assembly. The dynamic coupling of these two events then drives conformational changes in substrate proteins during cellular processes that involve protein unfolding and protein-complex remodeling, such as proteolysis, membrane fusion, DNA replication, and microtubule sliding [102-105]. Based on structure-function analysis of several AAA+ proteins, it has been proposed that residues extending from each subunit into the central pore formed by the hexamer are involved in substrate binding and translocation through the pore during processing [106-108].

The predicted structure of ANCCA includes a bromodomain located C-terminal to two centrally situated AAA+ domains that are most closely related in sequence homology to the so-called classic clade of AAA+ proteins such as p97/VCP [99-100]. Our work suggest that ANCCA is involved in the recruitment or assembly of transcriptionally active protein complexes including CBP on target genes and hence the histone modifications mediated by these complexes [99-100]. ANCCA is recruited to the promoters of specific subsets of ER or AR target genes with known functions in cell proliferation and survival, and its depletion impairs their hormone-induced expression. In the case of the ER target gene promoters, ANCCA is also necessary for estrogen stimulated CBP recruitment and chromatin histone H4 hyperacetylation. Interestingly, expression of ANCCA itself is robustly induced by estrogen and androgen in breast and prostate cancer cells respectively [99-100].

Although the mechanism by which ANCCA contributes to tumorigenesis is still largely unexplored, our studies and others support the notion that ANCCA plays important roles in the proliferation and survival of cancer cells, likely through its direct regulation of target genes. RNAi-mediated knock-down studies demonstrated that ANCCA promotes G1-S cell cycle progression of estrogen-stimulated breast cancer cells and survival of androgen-dependent or hormone-refractory prostate cancer cells [99-100]. Furthermore, high levels of ANCCA have been found in a significant percentage of breast and prostate cancer specimens, and its overexpression is associated with higher grade and disease recurrence [100-101, 109 and Kalashnikova E. et. al., Cancer Research, 2010, in press]. These findings, along with other studies identifying ANCCA as part of an aberrant gene expression profile in breast tumors, underscore the value of examining ANCCA as a potential therapeutic target [110-114].

Potential strategies for targeting ANCCA in cancer will likely depend on further structural and functional characterization, as well as elucidating the roles of relevant domains in NR coactivation. We demonstrated that ANCCA binds and hydrolyzes ATP [99] and our preliminary data suggests that ANCCA forms multimers (unpublished data). Interestingly, mutating key residues of the Walker A and Walker B motifs in the first AAA+ domain disrupt ANCCA function as an ER coactivator, indicating the critical involvement of ATPase activity [99]. Integrity of the bromodomain, which is often found in both HAT containing and ATP-dependent chromatin remodeling proteins [115], also affects the ability of ANCCA to function as a coactivator (Revenko A. et. al., Molecular and Cellular Biology, 2010, in press). Based on other AAA+ proteins, mutation of a key arginine residue in the conserved SRH element impairs oligomerization and ATPase activity [116]. This approach may be appropriate to determine whether ANCCA multimer assembly is required for its coactivator function. Alternatively, structural determinants responsible for ANCCA-NR interaction could be identified and targeted for specific disruption of ANCCA-mediated coactivation. For example, ANCCA directly associates with the DBD-hinge region of AR primarily through an N-terminal region that lies outside the first AAA+ domain [100].

3. Corepressors – Structure, function and therapeutic implications

3.1. NCoR and SMRT – Repressors of unliganded and antagonist-bound NRs

The first NR corepressors were identified based on their ability to mediate transcriptional repression by unliganded thyroid hormone (TR) and retinoid acid receptors. The aptly named NR corepressor (NCoR) and silencing mediator for RAR and TR (SMRT) contain multiple repression domains that serve as docking platforms for recruitment of additional components in the corepressor complex including HDAC and mSin3. Later studies discovered that NCoR and SMRT can interact with additional NRs in the absence of hormone - including vitamin D receptors and PPARs – or in the presence of antagonists – such as ER, AR, glucocorticoid receptor, and progesterone receptor (reviewed in [117] and see section 2.1.3). These findings imply that NCoR and SMRT are specifically involved in active repression by NRs when they are not bound by agonist hormones. However, the ability to associate with NCoR and SMRT is also influenced by factors that can change the accessibility of corepressor docking sites on the NR. These include receptor isoform and

heterodimer composition (i.e. for RAR), as well as DNA binding sequence and interactions with other transcription factors at the promoter [117].

The NR interaction domains located in the C-terminus of NCoR and SMRT consist of helical motifs known as corepressor NR (CoRNR) boxes with the consensus sequence L/I-X-X-I/V-I or LXXXI/LXXXI/L. Differences in affinity for NRs are affected by sequence variations in the CoRNR box motif itself, adjacent amino acids, and the corepressor binding surface of the receptor [117-118]. Interestingly, alternative splicing of SMRT generates isoforms with different affinities for different receptors [119]. In analogous to the coactivator NR box, the CoRNR box interacts with residues found in helices 3, 5 and 6 of the LBD hydrophobic groove [118]. However, as previously discussed, the ligand-dependent positioning of helix 12/AF-2 relative to the LBD determines whether coactivator or corepressor can bind. In the unliganded receptor, the extended conformation of helix 12 away from the LBD removes steric restraints that would otherwise prevent the CoRNR box from binding [120]. By contrast, repositioning of helix 12 close to the LBD in the presence of agonist switches the steric accessibility of the binding surface to accommodate the shorter coactivator NR box. Another study using corepressor peptide mimics indicated that helix 12 contains a CoRNR box that can also compete for corepressor binding [121]. This finding provides an alternative explanation for the poor interaction between AF-2 and NCoR/SMRT in the agonist-bound receptor conformation. More recently, however, new receptor interaction motifs were identified at the N-terminus of SMRT and NCoR, and surprisingly the motifs interact with the DNA binding domain of receptors such as ERa, underscoring the complexity of corepressor-receptor interaction [122].

3.2. RIP140 and LCoR – Repressors of agonist-bound NRs

Since the discovery of NCoR and SMRT, the number of identified corepressors has expanded to include several diverse proteins that are distinguished structurally and functionally in their mechanism of repression (reviewed in [120]). Most of these recently described corepressors possess LXXLL NR boxes and can thus associate with the AF-2 of agonist-bound NRs. A few, such as NSD1 and COPR1, contain both activation and repression domains, as well as distinct NR interaction domains that function in the absence or presence of ligand depending on the target receptor [120]. The majority of NR box-containing corepressors, such as RIP140 and LCoR, contain only repression domains and inhibit agonist-activated NRs in a LXXLL-dependent manner [123-124]. Although RIP140 was initially identified as a coactivator depending on the cell and promoter context [117], it is now generally considered a corepressor. Both RIP140 and LCoR are widely expressed in human tissue and have been found to interact with and negatively regulate a large number of ligand-activated NRs [124 -125]. Gene knockout studies in mice suggest that RIP140 plays crucial roles in energy homeostasis and female fertility [126-127].

A distinguishing feature in corepressors of agonist-bound NRs is their ability to repress transcription through HDAC-dependent and –independent mechanisms in a receptor-dependent manner. For RIP140 and NCoR, this property may be mediated in part by secondary corepressors C-terminal-binding protein (CtBP) 1 and 2, which associate with ancillary mediators of repressive histone modifications including histone deacetylases such

as HDACs/mSin3 and histone methyl transferases such as G9A, Eu-HMT, and PcG/polycomb complex proteins [128-129]. Recruitment of HDAC6 to a central region in LCoR appears critical for its blocking of gene expression by agonist bound progesterone receptor and ERα [130-131]. The complexity and multiplicity of repressor domains present in a single corepressor protein indicates that corepressors may utilize diverse mechanisms to attenuate the transcriptional activation by NRs.

3.3. Clinical Significance of Corepressors as Therapeutic Targets

Mutations that alter specific NR interactions with corepressors such as NCoR and SMRT have been implicated in the pathogenesis of several forms of human endocrine disorders and malignancies. For example, such mutations in the isoforms of thyroid hormone receptors are initiated with the resistance to thyroid hormone (RTH) syndrome, hepatocellular carcinoma, renal carcinoma, and papillary thyroid cancer while mutations in PPAR-γ are associated with familial severe insulin resistance [117, 132-136]. These genetic lesions typically produce dominant-negative NRs that exhibit impaired release of corpressors in response to ligand and consequently interfere with the transcriptional activation by wild-type receptors.

On the other hand, changes in the level of specific corepressors or activity of HDACs that are recruited by corepressors have been implicated in inflammatory and malignant diseases [137-141]. The involvement of metastasis-associated (MTA) proteins in diverse transcriptional programs that regulate breast cancer progression indicates its potential value as a therapeutic target [142-144]. One promising study used small peptides to mimic the function of MTA1s, a short splice-variant of MTA1 with a unique NR box motif that sequesters ERα in the cytoplasm [145]. The MTA1s peptide containing the motif inhibited ER transactivation, estrogen-dependent proliferation, anchorage-independent growth and in vivo tumor progression of MCF7 cells [146]. Nonetheless, more in vivo studies will be needed to assess the therapeutic efficacy of targeting MTA and other corepressor proteins in tumors of various tissues. Ultimately, this type of investigation should also shed light on the critical roles of different corepressor proteins in cancer progression.

4. Concluding Remarks

Substantial research progress in NR coregulator function and mechanisms provided valuable insights into their contributions to disease development. This review focused on thus far relatively well-characterized representatives from both classes of coregulators and coincidentally, the evidence we present here attribute to their pathological and clinical relevance in various malignancies. However, as illustrated by the coactivator PGC-1α, some coregulators have established roles in physiological processes that are deregulated in other types of disease. Moreover, the widespread tissue distribution of various NR coactivators such as p160/SRC family members and corepressors NCoR and SMRT indicates that they are involved in regulating a diverse array of normal physiological functions as well. Indeed, tissue culture and animal models combined with human studies strongly suggest that altered expression and function of an expanding number of coregulators underlies the etiology of many pathological conditions involving metabolism, neurodegeneration, and hormonal disturbances.

While many clinical studies support the prognostic significance of coregulator expression in diseased tissues, studies that explore the potential of specific coactivators and corepressors as molecular targets are needed to expedite development of new drugs for treating or preventing hormone-related diseases. It is now evident that altered NR structure and function alone cannot explain the development or progression of relevant diseases. Thus, therapeutic strategies to target disease-promoting pathways with focus on modulating the expression or activity of specific coregulators can be viable and effective as well. However, as the function of coregulators is still being elucidated and new coregulators are being identified, targeting coregulators for new therapeutics represents both a new opportunity and enormous challenge. The latter lies in the complex gene networks regulated by the coregulators and also in their function as integrators for multiple, distinctive cell signaling pathways. Therefore, success of any targeting strategy will likely depend on deeper insights into the downstream pathways and gene networks that are regulated by specific coregulators, as well as the role played by post-translational modifications of chromatin and coregulators themselves. Nonetheless, given their crucial functions revealed, coregulators that possess well-defined functional motifs and/or enzymatic activities can be readily exploited for identification of compounds with therapeutic potential. The fact that some of the coregulators play important roles in hormone responsive and non-responsive diseases can make the effort in targeting them more rewarding.

Acknowledgments

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Abbreviations

NR	nuclear hormone receptor
LBD	ligand binding domain

|	
DBD	DNA binding domain
SERM	selective estrogen receptor modulator
SRC	steroid receptor coactivator
ACTR	activator for receptors
AIB1	amplified in breast cancer 1
TIF2	transcriptional intermediary factor 2
PGC-1	PPAR gamma coactivator-1
HAT	histone acetyltransferase
CARM1	coactivator-associated arginine methyltransferase 1
PRMT	protein arginine methyltransferase
ANCCA	AAA nuclear coregulator cancer-associated
AAA	ATPases associated with various cellular activities
SMRT	silencing mediator for RAR and TR
NCoR	NR corepressor
MTA	metastasis-associated protein
RIP140	receptor-interacting protein 140
LCoR	ligand-dependent corepressor
JMJD	jumonji C domain-containing histone demethylase
LSD1	lysine-specific histone demethylase 1
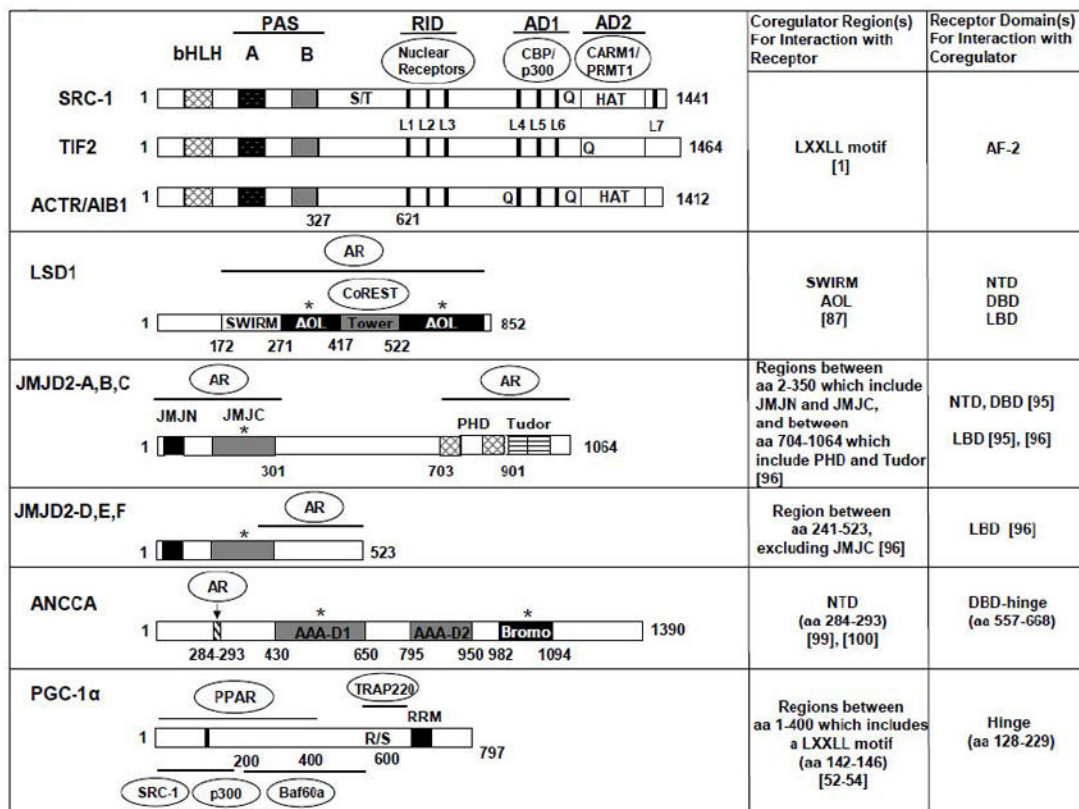
Fig 1.

The functional domains of coactivators featured in the review and their involvement in interactions with nuclear receptors and secondary coregulators. The locations of conserved structural and functional domains for the full-length human coactivator proteins are indicated by filled or textured boxes and bars, with amino acid residues numbered. bHLH, basic helix-loop-helix; PAS, Per/ARNT/Sim domain; S/T, serine/threonine-rich regions; RID, receptor interaction domain; L1–L6 (L7), LXXLL alpha-helix motifs, indicated by the black vertical lines;Q, glutamine-rich regions; HAT, histone acetyltransferase domains; AD1 and AD2, transcriptional activation domains; AR (androgen receptor); AOL (amine oxidase-like); JMJ (Jumonji); PHD (plant homeodomain); AAA (ATPases associated with various cellular activities); R/S (arginine/serine-rich region); RRM (RNA recognition motif). Interaction partners for RID, AD1, and AD2 are outlined inside ovals in the schematic for the three p160 coactivators. For the remaining coactivators, the domains highlighted by the lines or arrow are involved in binding the indicated NR or secondary coactivator, and the corepressor CoREST binds the Tower domain in LSD1. TRAP220 is the PPARγ-interacting subunit of TRAP/DRIP/Mediator complex. Baf60a is a core subunit of the SWI/SNF complex. * indicates that the domain's presence or activity is required for coactivation function. References in [] are included in the table specifying interactions for each NR-coactivator pair.
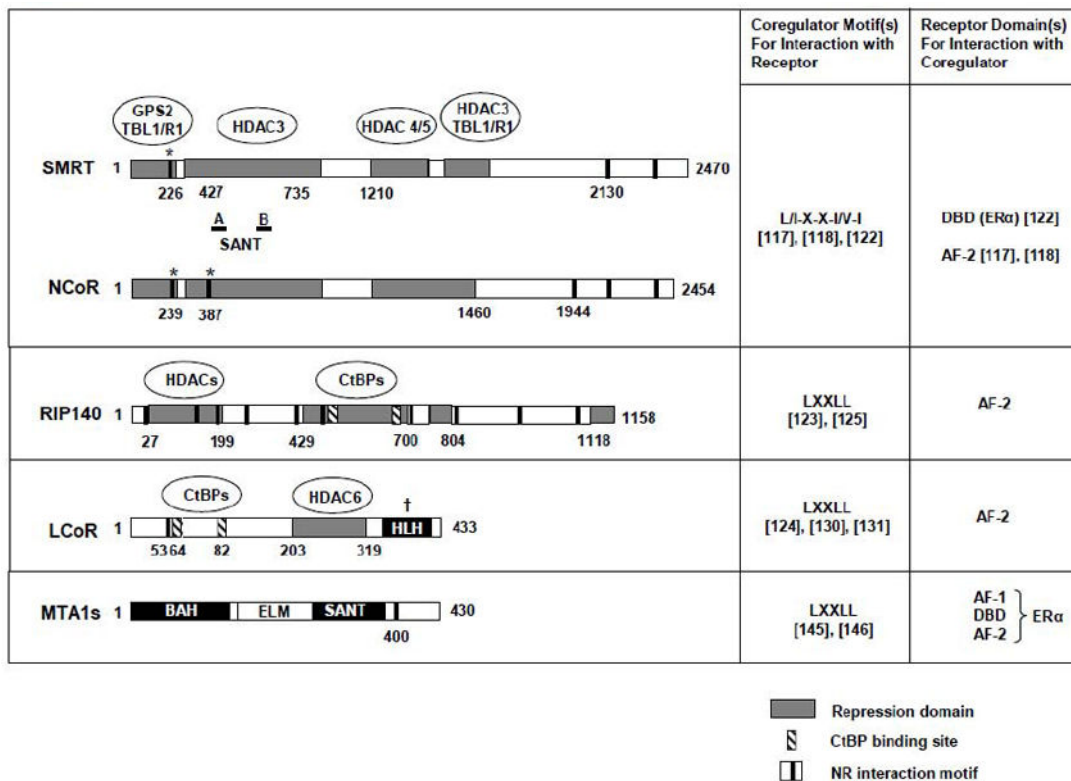
Fig 2.
The functional domains of corepressors featured in the review and their involvement in interactions with nuclear receptors and secondary corepressors. The transcriptional repression and NR interaction domains are indicated by gray-filled bars and black vertical lines, respectively, with associated secondary corepressors outlined inside the ovals. Other structural domains are indicated by black or white-filled bars, with amino acid residues numbered. The location of conserved SANT domains A and B in NCoR and SMRT are marked by the horizontal lines. The approximate location of CtBP binding sites are indicated in striped vertical bars. With the exception of MTA1s, the schematics for all corepressors represent full-length isoforms. * indicates recently identified NR interaction domains that bind the DBD in ERα. † indicates a required domain for corepression function. SANT (SWI3, ADA2, N-CoR and TFIIIB DNA binding domain); HLH (helix loop helix); BAH (bromo-adjacent homology); ELM (Egl-27 and MTA1 homology). The consensus NR interaction motif sequences for each corepressor are reported on the right along with the NR domain(s) that they bind and relevant references in [].