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Review

Transcriptional coregulators of the nuclear receptor superfamily: coactivators and corepressors

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Abstract. Nuclear receptors, many of which undergo a major conformational change upon binding specific ligand, belong to a superfamily of proteins that bind to specific DNA sequences and control gene transcription. They regulate the assembly of a transcriptional preinitiation complex at the promoter of target genes and modulate their expression in response to ligand. In particular, nuclear receptors repress or stimulate transcription by recruiting corepressor or coactivator proteins, in addition to directly contacting the basal transcription machinery. In this review, we discuss recent progress in studies of these transcriptional coregulators of nuclear receptors.

Key words. Nuclear receptor; transcription; coactivator; corepressor.

Introduction

Over 150 members of the nuclear receptor superfamily [reviewed in ref. 1] have been discovered since glucocorticoid receptor was first reported in 1985. They primarily regulate, in a ligand-dependent manner, transcriptional initiation of target genes by directly binding to specific DNA sequences named hormone response elements (HREs). The C terminus of the ligand-binding domain (LBD) of these proteins harbors an essential ligand-dependent transactivation function, activation function 2 (AF2), whereas the N terminus of many nuclear receptors often includes activation function 1 (AF1). Genetic studies have shown that transcription coregulators (or cofactors) with no specific DNA-binding activity are essential components of transcriptional regulation, leading to the identification of a series of nuclear receptor-interacting coregulatory proteins [for recent reviews, see refs 2–5]. These include the p160 family, CREB-binding protein (CBP)/p300, p/CAF, thyroid hormone receptor (TR)-associated protein (TRAP)/vitamin D3 receptor (VDR)-interacting protein (DRIP), activating signal cointegrator-1 (ASC-1), activating signal cointegrator-2 (ASC-2), TIF1, ARA70, SRA, PGC-1, Smad3, REA, RIP140, and many others. Thus far, these proteins have been shown to exhibit a few characteristic features, as summarized in figure 1. First, they bind to target transcription factors in a ligand-dependent manner. Second, many of them are capable of directly interacting with the basal transcriptional machinery. Third, some of them exhibit enzymatic function intrinsically linked to gene regula-

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tion, such as the nucleosome-modifying histone acetyl transferase (HAT) or deacetylase (HDAC) activities. In addition, they often harbor transferable transactivation or repression domains. Thus, these proteins appear to function by either remodeling chromatin structures and/or acting as adapter molecules between nuclear receptors and the components of the basal transcriptional apparatus. In this article, we focus on a number of coregulatory proteins whose functions with nuclear receptors are relatively well defined, along with ASC-1 and ASC-2, two coactivators newly reported from our laboratory.

The p160 family

A group of related proteins named the p160 or steroid receptor coactivator (SRC) family were found to enhance the ligand-induced transactivation function of several nuclear receptors. These proteins are grouped into three subclasses based on their sequence homology; i.e., SRC-1/NCoA-1 [6–8], TIF2/GRIP1/NCoA-2 [6, 7], and p/CIP/ACTR/AIB1/xSRC-3 [8–11]. A distinctive structural feature of the p160 coactivators is the presence of multiple LXXLL signature motifs [8, 12]. The AF2 core (helix 12) was recently shown to undergo major restructuring upon ligand binding, forming part of a 'charged clamp' that accommodates p160 coactivators within a hydrophobic cleft of the receptor LBD, through direct contacts with these LXXLL motifs [13, 14]. Loss-of-function studies using an antibody microinjection technique suggested that the p160 family proteins are required for nuclear receptor functions in vivo [8]. In addition, these factors can interact with CBP/p300 via a separate domain [15, 16]. Weak intrinsic HAT activity has been reported in SRC-1 and ACTR, suggesting that a function of these factors may involve chromatin remodeling [9, 17]. Interestingly, a novel arginine methyltransferase enzyme named CARM1 was found to be associated with the C-terminal region of p160 coactivators, which can methylate histone H3 in vitro [18]. These results suggest that coactivator-mediated methylation of proteins in the transcription machinery may contribute to transcriptional regulation. Finally, we have recently shown that SRC-1 also mediates transactivation by a series of other non-receptor-type transcription factors, including AP-1 [19], NFκB [20], SRF [21], and p53 [22]. In particular, SRC-1 and p/CIP were strong coactivators for p53, whereas AIB1 and xSRC-3 were repressive [22]. The p160 family of proteins also has a large number of uncharacterized isoforms [9; our unpublished results]. These results suggest a provoking hypothesis that each member of the p160 family or isoforms may differentially regulate a specific set of target transcription factors in vivo.

CBP/p300

CBP was originally isolated on the basis of its association with CREB in response to cAMP signaling, whereas its close homologue p300 was purified as a cellular binding protein of the adenoviral protein E1A [23, 24]. CBP and p300 have been implicated in functions of a large number of regulated transcription fac-

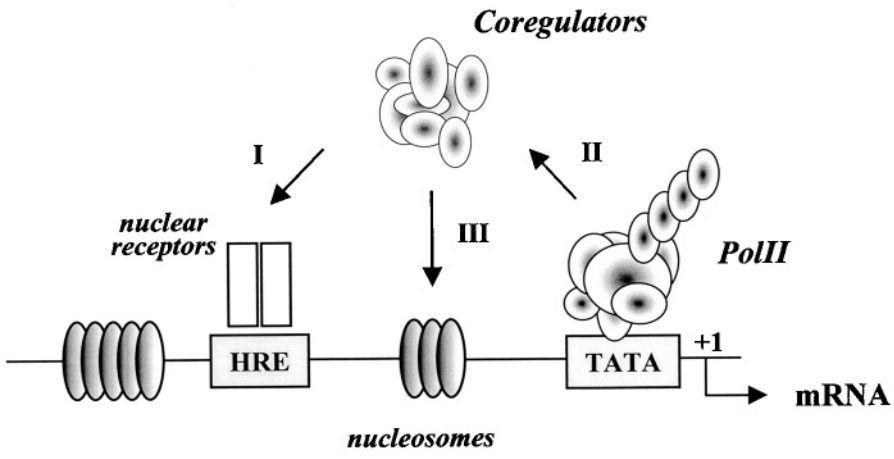

Figure 1. The role of transcriptional coregulators. Three general functions of known receptor coregulators are denoted as I, II, and III (see text for details). HRE and +1 denote hormone response elements and transcription initiation site, respectively. Nuclear receptors, nucleosomes, coregulator and RNA polymerase II bound to TATA sequences are schematically depicted. Notably, RNA polymerase II and most coregulators exist as a steady-state complex of multiple polypeptides [62].

tors [reviewed in ref. 25]. For nuclear receptors, the interaction with CBP/p300 is ligand and AF2 dependent, although this direct interaction does not appear to be essential for many nuclear receptors [26, 27]. In fibroblasts isolated from a $p300^{-/-}$ mouse, however, retinoic acid-dependent transcription was severely impaired, clearly indicating that CBP/p300 are components of hormonal regulation of transcription in vivo [28]. Surprisingly, CBP and p300 harbor HAT activity [29, 30]. In addition, purified p300 was shown to potentiate ligand-induced function of the estrogen receptor (ER) only on chromatinized template, strongly indicating that a major function of CBP/p300 could be to modify chromatin structure via histone acetylation [31]. However, it is notable that CBP/p300 can also acetylate and functionally modulate, either in a negative or positive manner, non-histone proteins, including TFIIEβ [32], HMG I(Y) [33], p53 [34], hematopoietic transcription factor GATA-1 [35], erythroid Krüppel-like factor [36], and ACTR [37]. These results suggest that CBP/p300 may also target different aspects of gene activation, in addition to their roles in chromatin remodeling.

p/CAF

This protein was first discovered on the basis of sequence homology to the yeast HAT protein Gcn5p [38]. The N terminus of p/CAF interacts with CBP and members of the p160 family, whereas the interaction interface between p/CAF and nuclear receptors differed from that mediating the binding with either CBP/p300 or p160s [39, 40]. A core p/CAF complex was recently isolated by exploiting an affinity purification approach, which contained human homologues of the yeast ADA proteins, TAFs or TAF homologues, and p/CAF-associated factor 65α which contains histone-like structure [41]. These results suggest a possible link between the p/CAF complex and the RNA polymerase II core machinery. This p/CAF complex resembles the GCN5/SAGA complex in yeast. In particular, other subunits of the complex facilitate p/CAF to acetylate histones in the context of nucleosomes, although p/CAF alone is inert [42].

TRAP/DRIP

TRAPs, comprising at least nine polypeptides, were immunopurified from cells stably transfected with Flag-tagged TR [43]. In reconstituted in vitro transcription assays utilizing naked DNA templates, the TRAP complex potentiated the transactivation function of liganded TR. A highly homologous VDR-interacting protein complex (i.e., DRIP) was also isolated using VDR as the affinity matrix [44], which in contrast to the p160 family of coactivators was devoid of any HAT activity [45]. Interestingly, constituents of the DRIP complex are almost identical to another newly discovered 'activator recruited cofactor complex,' which is essential for a number of other transcription factors such as SREBP, NFκB and VP16 [45, 46]. This TRAP/DRIP complex is recruited to the LBD AF2 core in response to ligand binding through a single subunit (DRIP205/TRAP220/TRIP2) via an LXXLL motif [45–47]. This protein anchors the other components of the DRIP/TRAP complex to the receptor, thereby conferring hormone-dependent recruitment of what appears to be a preformed complex. In addition, TRAP/DRIP also contain part of the 'mediator complex' [48], strongly suggesting their direct connection to the RNA polymerase II core machinery.

ASC-1

We have recently reported a novel nuclear receptor-interacting coactivator, ASC-1 [49]. As depicted in figure 2A, ASC-1 contains a zinc finger-like domain that harbors an autonomous transactivation function and binds to basal transcription factors TBP and TFIIA and transcription coactivators SRC-1 and CBP/p300. Intriguingly, ASC-1, a nuclear protein, was found to be cytoplasmic under serum deprivation but remained in the nucleus when serum starved in the presence of either ligand or overexpressed CBP/SRC-1, suggesting additional roles for ASC-1 in cellular signal transductions [49]. Recently, we purified the steady-state ASC-1 complex from HeLa nuclei, and found it to consist of four different polypeptides of 200, 100, 65 (ASC-1), and 50 kDa [our unpublished results]. Isolation of their cDNAs revealed that P200 and P50 have multiple RNA-helicase domains and RNA-binding motifs, respectively. In addition, we have recently isolated a new coactivator molecule ASC-3, which functions specifically with the ER and AP-1 [our unpublished results]. Interestingly, ASC-3 contains an RNA-binding motif and a serine/arginine-rich domain associated with many splicing factors [50]. Notably, p68 RNA helicase was recently isolated as a transcriptional coactivator specific for the AF1 of ERα [51], whereas RNA helicase A was found to mediate association of CBP with RNA polymerase II [52]. In addition, a novel transcriptional coactivator p52 interacted not only with transcriptional activators and general transcription factors to enhance activated transcription but also with the essential splicing factor ASF/SF2 both in vitro and in vivo to modulate ASF/SF2-mediated pre-mRNA splicing [53]. More recently, PGC-1 was shown to mediate direct coupling of transcription initiation and mRNA processings in vivo [54]. It is important to note that post-transcriptional

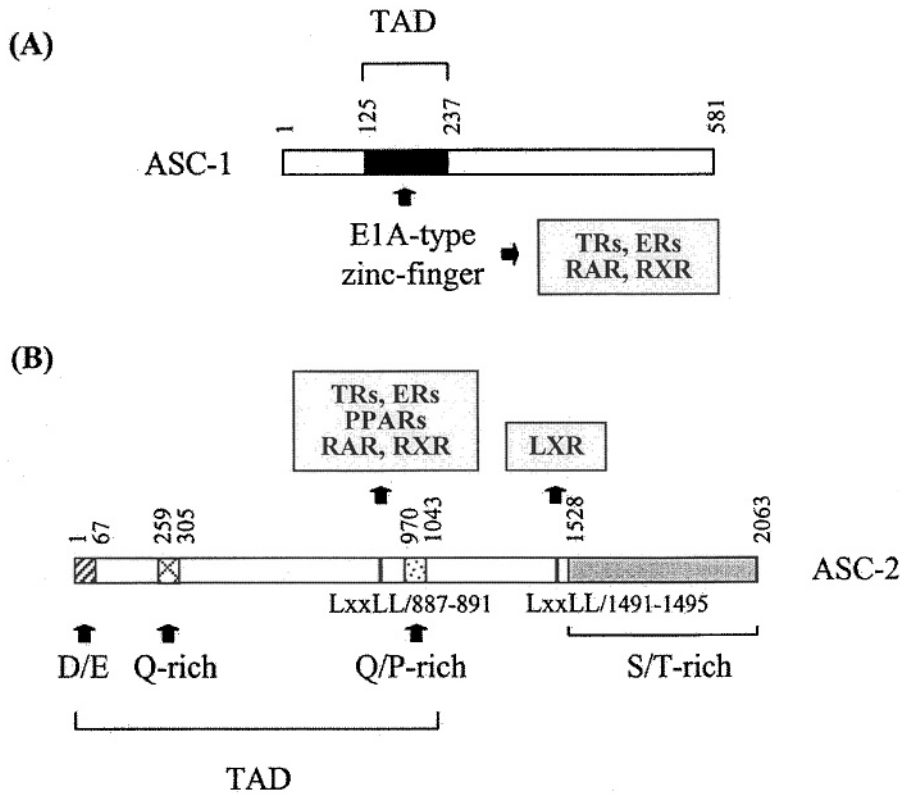

Figure 2. Schematic representations of ASC-1 and ASC-2. (*A*) The putative E1A-type zinc finger domain of ASC-1 is as depicted, and serves as an interaction interface with indicated nuclear receptors and also contains an autonomous transactivation domain (TAD) [49]. (*B*) Various functional domains of ASC-2 as well as its CBP-dependent TAD are as shown. ASC-2 contains two distinct LXXLL motifs that differentially recognize different nuclear receptors, as indicated [61].

mRNA processing such as 5′-capping, splicing, and polyadenylation can take place cotranscriptionally in vivo [reviewed in ref. 55]. Thus, these results suggest that, in addition to functioning as transcriptional coactivators, these proteins, including ASC-1, may also act as adaptor molecules to coordinate various pre-mRNA processing and transcriptional initiation of class II genes.

ASC-2

ASC-2 is another novel transcriptional coactivator molecule of nuclear receptors that we have recently isolated [56] (fig. 2B). Similar or identical molecules have also been reported by other groups, and variously named TRBP [57], PRIP [58], RAP250 [59], and NRC [60]. ASC-2 binds not only basal transcription factors TBP and TFIIA but also transcription coactivators SRC-1 and CBP/p300. Accordingly, ASC-2, a typical ligand- and AF2-dependent interacting protein of nuclear receptors, enhances receptor transactivation, either alone or in conjunction with SRC-1 and p300. Consistent with an idea that ASC-2 is essential for nuclear receptor function in vivo, microinjection of anti-ASC-2 antibody almost completely abrogated the ligand-dependent transactivation of retinoic acid receptor (RAR) [56]. Interestingly, the autonomous transactivation domain of ASC-2 coincided with the interaction interface with CBP, and the receptor-activating function of ASC-2 required the integrity of CBP recruitment in vivo [60, 61]. More recently, we have also found that ASC-2 exists as a stable complex of multiple polypeptides in vivo [unpublished results], which shows distinct chromatographic profiles from either ASC-1 [our unpublished results] or the recently described CBP/p300, SRC-1, and TRAP/DRIP complexes [43, 44, 62]. In addition, the LXXLL-type receptor interaction domains of ASC-2 acted as a potent dominant negative mutant of the peroxisome proliferator-activated receptors, RAR, TR, and liver X receptor transactivation [58, 61]. These results suggest that ASC-2 should bind directly to receptors and recruit CBP to mediate the receptor

transactivation function in vivo. Surprisingly, ASC-2 was identical to AIB3, a gene previously identified along with the p160 family member AIB1 during a search for genes amplified and overexpressed in breast and other human cancers [10, 63]. Similarly, high levels of PBP/TRAP220 expression and its gene amplification were also detected in primary breast cancers and breast cancer cell lines [64]. Whether overexpression of these genes directly results in tumorigenesis is not currently clear. However, overexpression of these genes could conceivably perturb normal signaling within the cell, which in turn may lead cells to engage in deregulated proliferative activity. Consistent with this idea, we have recently found that ASC-2 mediates transactivation by a series of mitogenic transcription factors, including SRF, AP-1, and NFκB [65].

NCoR/SMRT/HDACs

Unliganded RAR and TR bind to their target genes and repress transcription. This basal repression is known to be mediated by the silencing mediator of RAR and TR (SMRT) [66] and nuclear receptor corepressor (NCoR) [67], originally isolated as factors associated with the hinge domain of these nuclear receptors in the absence of ligand. More recently, however, the molecular basis of NCoR/SMRT recruitment was shown to be similar to that of coactivator recruitment, involving cooperative binding of two helical interaction motifs within the NCoR carboxyl terminus to both subunits of an RAR-retinoid X receptor (RXR) heterodimer [68, 69]. The NCoR/SMRT nuclear receptor interaction motifs exhibited a consensus sequence of LXXI/HIXXXI/L, representing an extended helix compared to the coactivator LXXLL helix [8, 12], which was able to interact with specific residues in the same receptor pocket required for coactivator binding. Thus, discrimination of the different lengths of the coactivator and corepressor interaction helices by the nuclear receptor AF2 motif may provide the molecular basis for the exchange of coactivators for corepressors, with ligand-dependent formation of the 'charge clamp' that stabilizes LXXLL binding and inhibits interaction of the extended corepressor helix. Interestingly, NCoR and SMRT harbor transferable repression domains that associate with various HDACs, consistent with the concept that histone hypoacetylation correlates with gene repression [70–75]. In humans, three highly homologous class I (HDAC1, HDAC2, HDAC3) and four class II (HDAC4, HDAC5, HDAC6, HDAC7) HDAC enzymes have been identified to date. The class I deacetylases HDAC1 and HDAC2 are components of multisubunit complexes (mSin3A and the NuRD complex) that are critically involved in the basal repression by unliganded TR and RAR [76, 77]. A few components of the NuRD complex are also present in the recently described Sin3 complex that consists of seven polypeptides [78, 79]. In particular, SAP30 was found to interact directly with NCoR [79]. It should be noted that NCoR/SMRT may serve as an adapter molecule between the core mSin3 complex and sequence-specific transcriptional repressors such as apo-nuclear receptors without stably associating with the mSin3 complex. More recently, however, SMRT/NCoR was found to be an active component of a newly isolated HDAC3 complex [72, 73]. NCoR/SMRT have also been reported to partner with HDAC4, HDAC5, and HDAC7 [74, 75]. Steroid hormone receptors do not appear to interact with NCoR or SMRT in the presence or absence of agonists, whereas both the ER and the progesterone receptor can interact with these corepressors in the presence of their respective antagonists [80–83]. Interestingly, NCoR/SMRT are also known to mediate transcriptional repression from a wide variety of other non-receptor-mediated pathways. These include AP-1, NFκB, SRF [84], MyoD [85], the bHLH-LZ proteins Mad and Mxi that mediate repression of myc activities and tumor suppression [86], E2F-repressive retinoblastoma protein [87], and the oncoproteins PLZF-RAR [88] and LAZ3/BCL6 [89], which are involved in acute promyelocytic leukemia and non-Hodgkin lymphomas, respectively.

Conclusion and perspectives

Transcription coactivators and corepressors provide important insights into the mechanisms by which ligand mediates the transactivation function of nuclear receptors. In brief, ligand binding results in the dismissal of HDAC-containing corepressor complexes and the concomitant recruitment of coactivator complexes. The current model for the coactivator recruitment by nuclear receptors involves a two-step mechanism, depicted in figure 3A. First, SRC-1 appears to be directly recruited to the liganded receptors, and then serves as a platform to recruit CBP. Consistent with this idea, the receptor-interacting LXXLL motif located at the N terminus of CBP was deleted without significantly affecting transactivation by RAR-RXR heterodimers, whereas the SRC-1 LXXLL motifs were absolutely essential [26, 27]. These factors and associated proteins such as p/CAF, by using their HAT activities, remodel the nucleosomal structures so that TRAP/DRIP complexes can replace SRC-1/CBP and bind the liganded receptors. Subsequent recruitment of RNA polymerase II complex to TRAP/DRIP completes the second step in nuclear receptor transactivation. However, this simple view is blurred by a large number of other nuclear

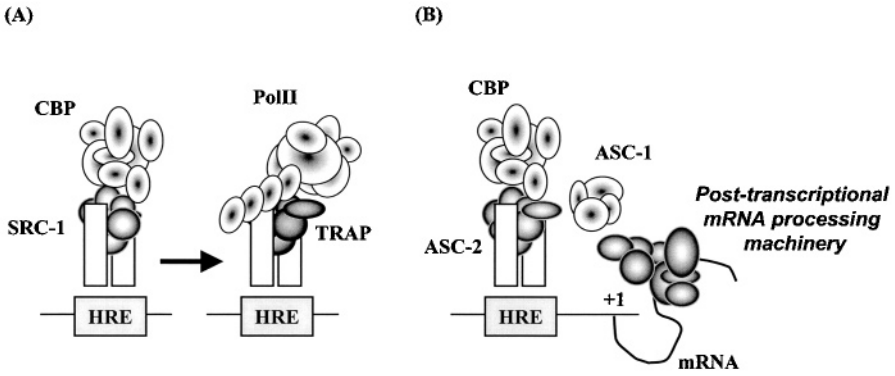

Figure 3. Model for coactivator assembly. (*A*) A two-step hypothesis for recruitment of coactivators represented schematically. SRC-1 binds receptors directly and serves as a platform to recruit CBP. When CBP and associated proteins, using their HAT activities, remodel the nucleosomal structures, TRAP/DRIP complexes occupy receptors and subsequently recruit the RNA polymerase II complex. (*B*) ASC-2 may act as an alternative, functional homologue of SRC-1, whereas ASC-1 and related factors may link post-transcriptional mRNA processing to transcriptional initiation (see text for details).

receptor-binding cofactor proteins or complexes, in particular the increasing number of AF2-dependent coactivators [2–5]. Thus, one of the most immediate challenges is to unravel the interrelationships between these distinct transcription cofactor proteins or complexes. These potential nuclear receptor cofactors may specifically function with different target genes as shown by the distinct roles of CBP and p300 in retinoid-induced differentiation of F9 cells [90]. Alternatively, these complexes may sequentially engage in different steps during ligand-induced transactivation by nuclear receptors. For example, we have recently suggested that ASC-2 may play a similar, essential role as SRC-1; i.e., direct binding to nuclear receptors and recruitment of CBP to the receptor-ASC-2 complex [61] (fig. 3B). Since ASC-2 expression is low in most cells but can be up-regulated in certain cells by various cytokines and growth factors [our unpublished results], ASC-2 may represent an inducible, alternative functional homologue of SRC-1. It should also be noted that, from the results with ASC-1 and ASC-3 [49; our unpublished results], p68 [51], RNA helicase A [52], p52 [53], and PGC-1 [54], transcription initiation appears to be directly linked to post-transcriptional RNA-processing events, as depicted in figure 3B. Finally, it is important to note that various cellular signal transduction pathways add another layer of regulation to the assembly and/or functions of these coregulatory proteins/complexes. In particular, phosphorylation of these coregulatory proteins may result in increased or decreased affinity with target transcription factors. For example, MAP kinase-induced phosphorylation of SRC-1 was recently demonstrated to enhance its ability to function as a transcriptional coactivator [91]. In addition, CBP- and HDAC4-mediated transcriptional regulation were shown to involve calcium signaling [92, 93]. More recently, a MEK-1 kinase pathway was demonstrated to regulate SMRT phosphorylation and nuclear export, resulting in inhibition of its corepressor function [94]. Further characterization of the coregulators specifically mentioned in this review as well as those newly emerging will continue to unravel the fundamental mechanisms underlying nuclear receptor action as well as the general transcription controls, undoubtedly with plenty of excitement and surprises.

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1 Mangelsdorf D. J., Thummel C., Beato M., Herrlich P., Schutz G., Umesono K. et al. (1995) The nuclear receptor superfamily: the second decade. Cell **83:** 835–839
2 Horwitz K. B., Jackson T. A., Bain D. L., Richer J. K., Takimoto G. S. and Tung L. (1996) Nuclear receptor coactivators and corepressors. Mol. Endocrinol. **10:** 1167–1177
3 McKenna N. J., Lanz R. B. and O'Malley B. W. (1999) Nuclear receptor coregulators: cellular and molecular biology. Endocr. Rev. **20:** 321–344
4 Glass C. K. and Rosenfeld M. G. (2000) The coregulator exchange in transcriptional functions of nuclear receptors. Genes Dev. **14:** 121–141
5 Robyr D., Wolffe A. P. and Wahli W. (2000) Nuclear hormone receptor coregulators in action: diversity for shared tasks. Mol. Endocrinol. **14:** 329–347
6 Hong H., Koli K., Garbedian M. J. and Stallcup M. R. (1997) GRIP1, a transcriptional coactivator for the AF-2 transactivation domain of steroid, thyroid, retinoid, and vitamin D receptors. Mol. Cell. Biol. **17:** 2735–2744

7 Voegel J. J., Heine M. J. S., Tini M., Vivat V., Chambon P. and Gronemeyer H. (1998) The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and -independent pathways. EMBO J. **17:** 507–519
8 Torchia J., Rose D. W., Inostroza J., Kamei Y., Westin S., Glass C. K. et al. (1997) The transcriptional co-activator p/CIP binds CBP and mediates nuclear-receptor function. Nature **387:** 677–684
9 Chen H. W., Lin R. J., Schilz R. L., Chakravarti D., Nash A., Nagy L. et al. (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. Cell **90:** 569–580
10 Anzick S. L., Kononen J., Walker R. L., Azorsa D. O., Tanner M. M., Guan X. Y. et al. (1997) AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. Science **277:** 965–968
11 Kim H.-J., Lee S.-K., Na S.-Y., Choi H. S. and Lee J. W. (1998) Molecular cloning of xSRC-3, a novel transcription coactivator from *Xenopus*, that is related to AIB1, p/CIP, and TIF2. Mol. Endocrinol. **12:** 1038–1047
12 Heery D. M., Kalkhoven E., Hoare S. and Parker M. G. (1997) A signature motif in transcriptional co-activators mediates binding to nuclear receptors. Nature **387:** 733–736
13 Nolte R. T., Wisely G. B., Westin S., Cobb J. E., Lambert M. H., Kurokawa R. et al. (1998) Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. Nature **395:** 137–143
14 Darimont B. D., Wagner R. L., Apriletti J. W., Stallcup M. R., Kushner P. J., Baxter J. D. et al. (1998) Structure and specificity of nuclear receptor-coactivator interactions. Genes Dev. **12:** 3343–3356
15 Kamei Y., Xu L., Heinzel T., Torchia J., Kurokawa R., Gloss B. et al. (1996) A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. Cell **85:** 403–414
16 Yao T. P., Ku G., Zhou N., Scully R. and Livingston D. M. (1996) The nuclear hormone receptor coactivator SRC-1 is a specific target of p300. Proc. Natl. Acad. Sci. USA **93:** 10626–10631
17 Spencer T. E., Jenster G., Burcin M. M., Allis C. D., Zhou J. X., Mizzen C. A. et al. (1997) Steroid receptor coactivator-1 is a histone acetyltransferase. Nature **389:** 194–198
18 Chen D., Ma H., Hong H., Koh S. S., Huang S. M., Schurter B. T. et al. (1999) Regulation of transcription by a protein methyltransferase. Science **284:** 2174–2177
19 Lee S.-K., Kim H.-J., Na S.-Y., Kim T. S., Choi H. S., Im S. Y. et al. (1998) Steroid receptor coactivator-1 coactivates activating protein-1-mediated transactivations through interaction with the c-Jun and c-Fos subunits. J. Biol. Chem. **273:** 16651–16654
20 Na S.-Y., Lee S.-K., Han S. J., Choi H. S., Im S. Y. and Lee J. W. (1998) Steroid receptor coactivator-1 interacts with the p50 subunit and coactivates nuclear factor kappaB-mediated transactivations. J. Biol. Chem. **273:** 10831–10834
21 Kim H.-J., Kim J. H. and Lee J. W. (1998) Steroid receptor coactivator-1 interacts with serum response factor and coactivates serum response element-mediated transactivations. J. Biol. Chem. **273:** 28564–28567
22 Lee S.-K., Kim H.-J. and Lee J. W. (1999) SRC-1 and its family members differentially regulate transactivation by the tumor suppressor p53. Mol. Endocrinol. **13:** 1924–1933
23 Chrivia J. C., Kwok R. P. S., Lamb N., Hagiwara M., Montminy M. R. and Goodman R. H. (1993) Phosphorylated CREB binds specifically to the nuclear protein CBP. Nature **365:** 855–859
24 Eckner R., Ewen M. E., Newsome D., Gerdes M., DeCaprio J. A., Lawrence J. B. et al. (1994) Molecular cloning and functional analysis of the adenovirus E1A-associated 300-kd protein (p300) reveals a protein with properties of a transcriptional adaptor. Genes Dev. **8:** 869–884
25 Goldman P. S., Tran V. K. and Goodman R. H. (1997) The multifunctional role of the co-activator CBP in transcriptional regulation. Recent Prog. Horm. Res. **52:** 103–120
26 Westin S., Kurokawa R., Nolte R. T., Wisely G. B., McInerney E. M., Rose D. W. et al. (1998) Interactions controlling the assembly of nuclear-receptor heterodimers and co-activators. Nature **395:** 199–202
27 Li J., O'Malley B. W. and Wong J. (2000) p300 requires its histone acetyltransferase activity and SRC-1 interaction domain to facilitate thyroid hormone receptor activation in chromatin. Mol. Cell. Biol. **20:** 2031–2042
28 Yao T. P., Oh S. P., Fuchs M., Zhou N. D., Ch'ng L. E., Newsome D. et al. (1998) Gene dosage-dependent embryonic development and proliferation defects in mice lacking the transcriptional integrator p300. Cell **93:** 361–372
29 Bannister A. J. and Kouzarides T. (1996) The CBP co-activator is a histone acetyltransferase. Nature **384:** 641–643
30 Ogryzko V. V., Schiltz R. L., Russanova V., Howard B. H. and Nakatani Y. (1996) The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell **87:** 953–959
31 Kraus W. L. and Kadonaga J. T. (1998) p300 and estrogen receptor cooperatively activate transcription via differential enhancement of initiation and reinitiation. Genes Dev. **12:** 331–342
32 Imhof A., Yang X. J., Ogryzko V. V., Nakatani Y., Wolffe A. P. and Ge H. (1997) Acetylation of general transcription factors by histone acetyltransferases. Curr. Biol. **7:** 689–692
33 Munshi N., Merika M., Yie J., Senger K., Chen G. and Thanos D. (1998) Acetylation of HMG I(Y) by CBP turns off IFN beta expression by disrupting the enhanceosome. Mol. Cell **2:** 457–467
34 Gu W. and Roeder R. G. (1997) Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell **90:** 595–606
35 Boyes J., Byfield P., Nakatani Y. and Ogryzko V. (1998) Regulation of activity of the transcription factor GATA-1 by acetylation. Nature **396:** 594–598
36 Zhang W. and Bieker J. J. (1998) Acetylation and modulation of erythroid Kruppel-like factor (EKLF) activity by interaction with histone acetyltransferases. Proc. Natl. Acad. Sci. USA **95:** 9855–9860
37 Chen H., Lin R. J., Xie W., Wilpitz D. and Evans R. M. (1999) Regulation of hormone-induced histone hyperacetylation and gene activation via acetylation of an acetylase. Cell **98:** 675–686
38 Yang X. J., Ogryzko V. V., Nishikawa J., Howard B. H. and Nakatani Y. (1996) A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1a. Nature **382:** 319–324
39 Blanco J. C. G., Minucci S., Lu J. M., Yang X. J., Walker K. K., Chen H. W. et al. (1998) The histone acetylase PCAF is a nuclear receptor coactivator. Genes Dev. **12:** 1638–1651
40 Korzus E., Torchia J., Rose D. W., Xu L., Kurokawa R., Mclnerney E. M. et al. (1998) Transcription factor-specific requirements for coactivators and their acetyltransferase functions. Science **279:** 703–707
41 Ogryzko V. V., Kotani T., Zhang X., Schlitz R. L., Howard T., Yang X. J. et al. (1998) Histone-like TAFs within the PCAF histone acetylase complex. Cell **94:** 35–44
42 Grant P. A., Duggan L., Cote J., Roberts S. M., Brownell J. E., Candau R. et al. (1997) Yeast Gcn5 functions in two multisubunit complexes to acetylate nucleosomal histones: characterization of an Ada complex and the SAGA (Spt/Ada) complex. Genes Dev. **11:** 1640–1650
43 Fondell J. D., Ge H. and Roeder R. G. (1996) Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. Proc. Natl. Acad. Sci. USA **93:** 8329–8333
44 Rachez C., Suldan Z., Ward J., Chang C. P., Burakov D., Erdjument-Bromage H. et al. (1998) A novel protein complex that interacts with the vitamin D3 receptor in a ligand-dependent manner and enhances VDR transactivation in a cell-free system. Genes Dev. **12:** 1787–1800
45 Rachez C., Gamble M., Chang C. P., Atkins G. B., Lazar M. A. and Freedman L. P. (2000) The DRIP complex and SRC-1/p160 coactivators share similar nuclear receptor bind-

ing determinants but constitute functionally distinct complexes. Mol. Cell. Biol. **20:** 2718–2726
46 Naar A. M., Beaurang P. A., Zhou S., Abraham S., Solomon W. and Tjian R. (1999) Composite co-activator ARC mediates chromatin-directed transcriptional activation. Nature **398:** 828–832
47 Lee J. W., Choi H. S., Gyuris J., Brent R. and Moore D. D. (1995) Two classes of proteins dependent on either the presence or absence of thyroid hormone for interaction with the thyroid hormone receptor. Mol. Endocrinol. **9:** 243–254
48 Kim Y. J., Bjorklund S., Li Y., Sayre M. H. and Kornberg R. D. (1994) A multiprotein mediator of transcriptional activation and its interaction with the C-terminal repeat domain of RNA polymerase II. Cell **77:** 599–608
49 Kim H.-J., Yi J. Y., Sung H. S., Moore D. D., Jhun B. H., Lee Y. C. et al. (1999) ASC-1, as a novel transcription coactivator of nuclear receptors, and its cytosolic localization under serum-deprivation. Mol. Cell. Biol. **19:** 6323–6332
50 Graveley B. R. and Maniatis T. (1998) Arginine/serine-rich domains of SR proteins can function as activators of pre-mRNA splicing. Mol. Cell **1:** 765–771
51 Endoh H., Maruyama K., Masuhiro Y., Kobayashi Y., Goto M., Tai H. et al. (1999) Purification and identification of p68 RNA helicase acting as a transcriptional coactivator specific for the activation function 1 of human estrogen receptor alpha. Mol. Cell. Biol. **19:** 5363–5372
52 Nakajima T., Uchida C., Anderson S. F., Lee C. G., Hurwitz J., Parvin J. D. et al. (1997) RNA helicase A mediates association of CBP with RNA polymerase II. Cell **90:** 1107–1112
53 Ge H., Si Y. and Wolffe A. P. (1998) A novel transcriptional coactivator, p52, functionally interacts with the essential splicing factor ASF/SF2. Mol. Cell **2:** 751–759
54 Monsalve M., Wu Z., Adelmant G., Puigserver P., Fan M. and Spiegelman B. M. (2000) Direct coupling of transcription and mRNA processing through the thermogenic coactivator PGC-1. Mol. Cell **6:** 307–316
55 Hirose Y. and Manley J. L. (2000) RNA polymerase II and the integration of nuclear events. Genes Dev. **14:** 1415–1429
56 Lee S.-K., Anzick S. L., Choi J. E., Bubendorf L., Guan X. Y., Jung Y. K. et al. (1999) ASC-2, a novel transcriptional coactivator of nuclear receptors and its amplification in human cancers. J. Biol. Chem. **274:** 34283–34293
57 Ko L., Cardona G. R. and Chin W. W. (2000) Thyroid hormone receptor-binding protein, an LXXLL motif-containing protein, functions as a general coactivator. Proc. Natl. Acad. Sci. USA **97:** 6212–6217
58 Zhu Y., Kan L., Qi C., Kanwar Y. S., Yeldandi A. V., Rao M. S. et al. (2000) Isolation and characterization of peroxisome proliferator-activated receptor (PPAR) interacting protein (PRIP) as a coactivator for PPAR. J. Biol. Chem. **275:** 13510–13516
59 Caira F., Antonson P., Pelto-Huikko M., Treuter E. and Gustafsson J. A. (2000) Cloning and characterization of RAP250, a novel nuclear receptor coactivator. J. Biol. Chem. **275:** 5308–5317
60 Muktar A. M. and Samuels H. H. (2000) A new family of nuclear receptor coregulators that integrate nuclear receptor signaling through CREB-binding protein. Mol. Cell. Biol. **20:** 5048–5063
61 Lee S.-K., Jung S.-Y., Na S.-Y., Lee Y. C. and Lee J. W. (in press) Two distinct nuclear receptor-interaction domains and CREB-binding protein-dependent transactivation function of activating signal cointegrator-2. Mol. Endocrinol.
62 McKenna N. J., Nawaz Z., Tsai S. Y., Tsai M. J. and O'Malley B. W. (1998) Distinct steady-state nuclear receptor coregulator complexes exist in vivo. Proc. Natl. Acad. Sci. USA **95:** 11697–11702
63 Guan X. Y., Xu J., Anzick S. L., Zhang H., Trent J. M. and Meltzer P. S. (1996) Hybrid selection of transcribed sequences from microdissected DNA: isolation of genes within amplified region at 20q11–q13.2 in breast cancer. Cancer Res. **56:** 3446–3450
64 Zhu Y., Qi C., Jain S., Le Beau M. M., Espinosa R. 3rd, Atkins G. B. et al. (1999) Amplification and overexpression of peroxisome proliferator-activated receptor binding protein (PBP/PPARBP) gene in breast cancer. Proc. Natl. Acad. Sci. USA **96:** 10848–10853
65 Lee S.-K., Na S.-Y., Jung S.-Y., Jhun B. H., Cheong J., Meltzer P. S. et al. (2000) Activating protein-1, nuclear factor-κB and serum response factor, as novel target molecules of the cancer-amplified transcription coactivator ASC-2. Mol. Endocrinol. **14:** 915–925
66 Chen J. D. and Evans R. M. (1995) A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature **377:** 454–457
67 Horlein A. J., Naar A. M., Heinzel T., Torchia J., Gloss B., Kurokawa R. et al. (1995) Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor corepressor. Nature **377:** 397–404
68 Perissi V., Staszewski L. M., McInerney E. M., Kurokawa R., Krones A., Rose D. et al. (1999) Molecular determinants of nuclear receptor-corepressor interaction. Genes Dev. **13:** 3198–3208
69 Hu X. and Lazar M. A. (1999) The CoRNR motif controls the recruitment of corepressors by nuclear hormone receptors. Nature **402:** 93–96
70 Heinzel T., Lavinsky R. M., Mullen T. M., Soderstrom M., Laherty C. D., Torchia J. et al. (1997) A complex containing N-CoR, mSin3 and histone deacetylase mediates transcriptional repression. Nature **387:** 43–48
71 Nagy L., Kao H.-Y., Chakravarti D., Lin R. J., Hassig C. A., Ayer D. E. et al. (1997) Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase. Cell **89:** 373–380
72 Wen Y. D., Perissi V., Staszewski L. M., Yang W. M., Krones A., Glass C. K. et al. (2000) The histone deacetylase-3 complex contains nuclear receptor corepressors. Proc. Natl. Acad. Sci. USA **97:** 7202–7207
73 Guenther M. G., Lane W. S., Fischle W., Verdin E., Lazar M. A. and Shiekhattar R. (2000) A core SMRT corepressor complex containing HDAC3 and TBL1, a WD40-repeat protein linked to deafness. Genes Dev. **14:** 1048–1057
74 Kao H. Y., Downes M., Ordentlich P. and Evans R. M. (2000) Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression. Genes Dev. **14:** 55–66
75 Huang E. Y., Zhang J., Miska E. A., Guenther M. G., Kouzarides T. and Lazar M. A. (2000) Nuclear receptor corepressors partner with class II histone deacetylases in a Sin3-independent repression pathway. Genes Dev. **14:** 45–54
76 Zhang Y., LeRoy G., Seelig H. P., Lane W. S. and Reinberg D. (1998) The dermatomyositis-specific autoantigen Mi2 is a component of a complex containing histone deacetylase and nucleosome remodeling activities. Cell **95:** 279–289
77 Tong J. K., Hassig C. A., Schnitzler G. R., Kingston R. E. and Schreiber S. L. (1998) Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex. Nature **395:** 917–921
78 Zhang Y., Sun Z. W., Iratni R., Erdjument-Bromage H., Tempst P., Hampsey M. et al. (1998) SAP30, a novel protein conserved between human and yeast, is a component of a histone deacetylase complex. Mol. Cell **1:** 1021–1031
79 Laherty C. D., Billin A. N., Lavinsky R. M., Yochum G. S., Bush A. C., Sun J. M. et al. (1998) SAP30, a component of the mSin3 corepressor complex involved in N-CoR-mediated repression by specific transcription factors. Mol. Cell **2:** 33–42
80 Xu J., Nawaz Z., Tsai S. Y., Tsai M. J. and O'Malley B. W. (1996) The extreme C terminus of progesterone receptor contains a transcriptional repressor domain that functions through a putative corepressor. Proc. Natl. Acad. Sci. USA **93:** 12195–12199
81 Jackson T. A., Richer J. K., Bain D. L., Takimoto G. S., Tung L. and Horwitz K. B. (1997) The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge domain-binding coactivator L7/SPA and the

corepressors N-CoR or SMRT. Mol. Endocrinol. **11:** 693–705
82 Smith C. L., Nawaz Z. and O'Malley B. W. (1997) Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. Mol. Endocrinol. **11:** 657–666
83 Lavinsky R. M., Jepsen K., Heinzel T., Torchia J., Mullen T. M., Schiff R. et al. (1998) Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes. Proc. Natl. Acad. Sci. USA **95:** 2920–2925
84 Lee S.-K., Kim J.-H., Lee Y. C., Cheong J. and Lee J. W. (2000) Silencing mediator of retinoic acid and thyroid hormone receptors, as a novel transcriptional corepressor molecule of activating protein-1, nuclear factor-κB and serum response factor. J. Biol. Chem. **275:** 12470–12474
85 Bailey P., Downes M., Lau P., Harris J., Chen S. L., Hamamori Y. et al. (1999) The nuclear receptor corepressor N-CoR regulates differentiation: N-CoR directly interacts with MyoD. Mol. Endocrinol. **13:** 1155–1168
86 Laherty C. D., Yang W. M., Sun J. M., Davie J. R., Seto E. and Eisenman R. N. (1997) Histone deacetylases associated with the mSin3 corepressor mediate mad transcriptional repression. Cell **89:** 349–356
87 Lai A., Lee J. M., Yang W. M., DeCaprio J. A., Kaelin W. G. Jr, Seto E. et al. (1999) RBP1 recruits both histone deacetylase-dependent and -independent repression activities to retinoblastoma family proteins. Mol. Cell. Biol. **19:** 6632–6641
88 Lin R. J., Nagy L., Inoue S., Shao W., Miller W. H. Jr and Evans R. M. (1998) Role of the histone deacetylase complex in acute promyelocytic leukemia. Nature **391:** 811–814
89 Dhordain P., Albagli O., Lin R. J., Ansieau S., Quief S., Leutz A. et al. (1997) Corepressor SMRT binds the BTB/POZ repressing domain of the LAZ3/BCL6 oncoprotein. Proc. Natl. Acad. Sci. USA **94:** 10762–10767
90 Kawasaki H., Eckner R., Yao T. P., Taira K., Chiu R., Livingston D. M. et al. (1998) Distinct roles of the co-activators p300 and CBP in retinoic-acid-induced F9-cell differentiation. Nature **393:** 284–289
91 Rowan B. G., Weigel N. L. and O'Malley B. W. (2000) Phosphorylation of steroid receptor coactivator-1: identification of the phosphorylation sites and phosphorylation through the mitogen-activated protein kinase pathway. J. Biol. Chem. **275:** 4475–4483
92 Hu S. C., Chrivia J. and Ghosh A. (1999) Regulation of CBP-mediated transcription by neuronal calcium signaling. Neuron **22:** 799–808
93 Youn H. D., Grozinger C. M. and Liu J. O. (2000) Calcium regulates transcriptional repression of myocyte enhancer factor 2 by histone deacetylase 4. J. Biol. Chem. **275:** 22563–22567
94 Hong S. H. and Privalsky M. L. (2000) The SMRT corepressor is regulated by a MEK-1 kinase pathway: inhibition of corepressor function is associated with SMRT phosphorylation and nuclear export. Mol. Cell. Biol. **20:** 6612–6625