

# Role of Steroid Hormone Coregulators in Health and Disease

M.K. Thakur V. Paramanik

Biochemistry and Molecular Biology Laboratory, Department of Zoology, Banaras Hindu University, Varanasi, India

## Key Words

Steroid hormone · Coactivators · Corepressors · Gene regulation · Diseases

## Abstract

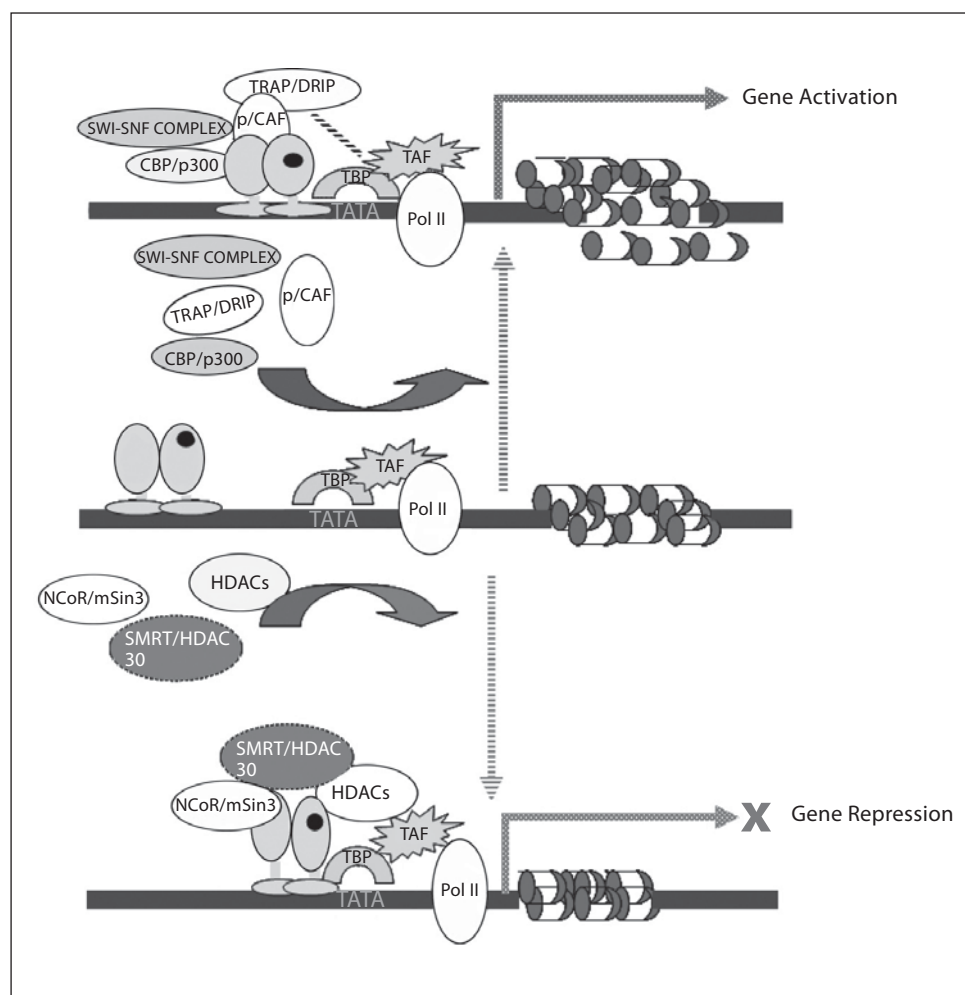
The involvement of coactivators and corepressors, collectively termed as coregulators, increases the complexity of regulation of steroid hormone action. Following the interaction of the steroid hormone-receptor complex with the specific nucleotide sequences of target genes, the coregulators are recruited for activation or suppression of specific genes. The coregulators regulate a number of hormonal events during pregnancy, sex differentiation, development, reproduction and sexual behavior. They also exert equally important functions in non-reproductive tissues like heart, kidney, pancreas, bone and brain. The mutation and/or aberrant expression of these coregulators affect the normal function of steroid hormones and result in physiological abnormalities leading to the development of diseases. Therefore, understanding the role of coregulators in steroid hormone action is important and would help in developing the therapeutic strategy for the treatment of steroid-related diseases. In this review article, we describe the coregulators and their implication in health and pathogenesis of diseases. Furthermore, the possible therapeutic approach has been discussed for the treatment of steroid-related diseases, which will be of future interest in the field of medical sciences.

Copyright © 2009 S. Karger AG, Basel

## Introduction

Steroid hormone action is mediated mainly through the intracellular nuclear receptors. These receptors are ligand-inducible transcription factors belonging to the nuclear receptor superfamily and mediate diverse actions of sex steroids. They share three common functional domains: (i) amino-terminal transactivation domain containing activation function (AF)-1, (ii) central or DNA-binding domain (DBD) containing two zinc fingers like motifs, and (iii) carboxy-terminal ligand-binding domain containing AF-2 [1]. Following the binding of hormone to its specific receptor, the binary complex interacts with the

ACTR = Activator of the thyroid and retinoic acid receptor; ARA = androgen receptor activator; ARIP = androgen receptor-interacting protein; BRG = Brahma-related gene; CBP = CREB-binding protein; CIZ1 = Cip-interacting zinc finger protein 1; CREB = cAMP-response element-binding protein; DAX-1 = DSS-AHC critical region on the chromosome gene 1; DRIP = vitamin D receptor-interacting protein; ERAP-140 = estrogen receptor (ER)-associated protein 140; ETO = eight-twenty-one translocation; GRIP = glucocorticoid receptor interacting protein; MeCP-2 = methyl-CpG-binding protein; NCoR = nuclear receptor corepressor; pCAF = p300/CBP-associated factor; pCIP = p300/CBP cointegrator-associated protein; PGC = PPAR $\gamma$  coactivator; RAC = receptor-associated coactivator; RIP = receptor-interacting protein; SMRT = silencing mediator of retinoic acid and thyroid hormone receptor; SRC = steroid receptor coactivator; TAF = TBP-associated factor; TBP = TATA-binding protein; TIF = transcriptional intermediary factor.



**Fig. 1.** Role of coregulators in gene regulation during steroid hormone action.

responsive elements of the target genes and recruits an array of *coregulators* and *chromatin modifiers*. The involvement of coregulators makes the regulation more complex (fig. 1). These coregulators are classified as *coactivators* when they activate the expression of genes and as *corepressors* when they inhibit the transcription of genes [2]. Previously, it was thought that *coactivators* and *corepressors* are present in separate complexes, but recent evidence indicates that these molecules exist in the same complex [3]. This complex has an opposite function and allows for efficient transcriptional control mechanisms depending on posttranslational modification of coregulators. In the majority of cases, transcription is activated by histone acetylation and repressed by histone deacetylation.

This review discusses the current understanding of coregulators and their mechanism of action, defects in coregulators, resulting diseases and therapeutic ap-

proaches. The information included in this review has been collected from the literature available in NCBI, ISI Web of Knowledge, ScienceDirect search engine, HighWire press and Karger press journals. Understanding the role of coregulators in steroid hormone action is important for developing a therapeutic strategy for the treatment of steroid-related diseases.

### Coactivators and Their Mechanism of Action

A large number of coactivators have been identified and characterized over the past few years [4] – several are listed in table 1. They are characterized by their interaction with the transcription machinery and activation function domains of nuclear receptors [5]. Based on the mechanism of function, coactivators can be categorized

**Table 1.** Coactivators and their interaction with nuclear receptors

Coactivators	Interaction	
	in vitro	in vivo
SRC	PR, RAR, RXR, TR	ER, GR, PR, TR, RXR
ERAP160/p160	ER, RAR, RXR	ER
GRIP1/TIF2	ER, AR, GR, TR, PR, RAR, RXR	ER, AR, GR, PR
SRC-2/NcoA-2	PPAR	VDR, RAR, RXR
ACTR/AIB1/RAC3	ER, PR, TR, VDR, RAR, RXR, VDR, PPAR	ER, PR, TR, RAR
p/CIP	ER, RAR	ER, PR, TR, RAR
ERAP140/P140	ER	not available
RIP140	ER, PPAR $\alpha$ , TR, RAR, RXR	ER
RIP160/P160	ER	not available
p/CAF	ER, AR, GR, RAR, RXR	RAR/RXR
CBP/P300	ER, GR, TR, RAR, RXR	ER, TR, RAR, RXR
ARA70	AR	AR, ER, GR, PR (weak)
Ada3	ER, TR, RXR	ER, RXR
Rap46	ER, AR, GR, AR, PR, TR	not available
GRIP170	GR	GR
PGC-1	ER $\alpha$ , PPAR $\gamma$ , RAR $\alpha$ , TR $\beta$	PPAR $\gamma$ /RAR $\alpha$ , TR $\beta$ /RXR $\alpha$
PGC-2	PPAR $\gamma$ , ER $\alpha$ , TR $\beta$	PPAR $\gamma$ , ER $\alpha$
SPT6	ER	ER
SW12/SNF2 (Brahma)	GR (SWI3), ER	ER, GR, RAR
SNURF	with DBD of AR,, ER, PR	AR
TRAP220	TR, VDR, RAR, RAR, RXR, PPAR $\alpha$ , PPAR $\gamma$ , ER	TR
TRAP100	ER, RXR, PPAR $\alpha$ , PPAR $\gamma$ , RAR and RXR associate with a different complex	VDR
DRIP	TR, VDR, PPAR $\gamma$	VDR
RAC3	AR, ER	AR, ER
NSD	ER, RXR	Bifunctional factor
	TR, RAR	Repression and activation
RSP5/RPF1	no direct interaction	GR, PR, but not ER
PGC-I	PPAR, liver X receptor	PPAR, liver X receptor
ARI4	AR	AR
CiZ/FHL2	ER $\alpha$	ER $\alpha$
Ubc9/PIAs	ER $\alpha$	ER $\alpha$

into three distinct multiprotein complexes: (i) *SWI/SNF complex*, which is associated with ATP-dependent alteration in chromatin structure; (ii) *p160/CBP complex*, which is primarily related to histone acetylation, and (iii) *mediator complex*, which is involved in the activation of RNA polymerase II and initiation of transcription.

*(i) SWI/SNF Complex and Chromatin Remodeling*

Members of the SWI/SNF family of coactivators are the first described positive regulators of hormone action. They were initially identified in the yeast on the basis of a genetic screening required for regulation of mating type switching [6]. They mediate chromatin remodeling of *swi/snf* genes and support glucocorticoid receptor (GR)-de-

pendent transactivation. However, mutations in these genes fail to transactivate a reporter gene in the presence of transfected GR. It has also been shown that GR co-immunoprecipitates with the SWI/SNF complex [7, 8]. Ligand-dependent transcriptional activation of GR or estrogen receptor (ER) requires several SWI gene products such as SWI1, SWI2 and SWI3, which are members of the SWI/SNF complex. The human homologue of SWI2 is termed as SNF2 $\alpha$  and SNF2 $\beta$  or Brahma [9, 10]. Other members of the SWI/SNF family include the yeast general control non-repressed protein (GCN) 5, p300 and CBP [11, 12]. They possess histone acetyltransferase (HAT) activity which is involved in chromatin remodeling.

**Table 2.** Corepressors and their interaction with nuclear receptors

Corepressors	Interaction	
	in vitro	in vivo
SMRT/TRAC-2	RAR, TR, v-ErbA, PPAR $\gamma$ , RXR (weak)	RAR, TR, PPAR $\gamma$
N-CoR/RIP13	TR, Rev Erb, RAR, PPAR $\gamma$	TR, Rev Erb, RAR
SUN-CoR	TR, Rev Erb	TR, Rev Erb
Ssn6/Tup1	Not available	ER, PR
TRUP	TR	TR, RAR
Calreticulin	GR, AR	GR, AR, RAR
REA	ER	ER
ZNF 366	ER $\alpha$	ER
RIP 140	AR, ER $\alpha$	AR, ER $\alpha$
MTA	ER $\alpha$	ER $\alpha$
NM23-H2	ER $\beta$	ER $\beta$
AIB	ER $\alpha$	ER $\alpha$

#### (ii) *p160/CBP and Histone Acetylation*

SRC-1, first discovered in human as a ligand-dependent protein of progesterone receptor (PR), belongs to the p160/CBP complex [13]. It interacts with helix 12 within AF-1 and AF-2 regions of ER [14]. The binding of SRC-1 is more efficient when it makes a bridge between AF-1 and AF-2 and interacts directly to the basal transcription machinery through TFII or TBP [15].

DRIP, purified previously as a member of the p160/CBP coactivator complex, has no HAT activity [16]. VDR interacts directly with a human multi-protein WINAC through the William syndrome transcription factor which contains both SWI/SNF components and DNA replication-related factors and exhibits ATP-dependent chromatin remodeling activity [17]. Another member of the p160/CBP complex, p300/CBP, interacts with roughly 100 proteins [18]. RAC3, also known as SRC-3/ACTR/AIB1/pCIP/TRAM-1, acts through a bipartite nuclear localization signal and importin  $\alpha$ 3 protein [19]. AIB (amplified in breast cancer) 1, a member of the p160 family, is highly expressed in ER- and PR-responsive endometrial carcinoma [20].

#### (iii) *Chromatin Modifiers and RNA Polymerase II*

Higher order chromatin structure is regulated in part by covalent modifications of N-terminal histone tails, which in turn serve as platforms for the recruitment of signaling molecules that include non-histone proteins such as heterochromatin protein (HP1), nucleosomal re-

modeling and histone deacetylation complex [21]. Translocated in liposarcoma (TLS), a 65-kDa protein has been identified as TFII/RNA polymerase II-associated protein because of its sequence similarity to hTAF68 [22]. Its high-affinity binding enhances the expression of thyroid receptor (TR) proteins. Furthermore, sumoylation is responsible for chromatin modification of AR interacting protein 4 (ARIP4), which belongs to the SNF2-like family and acts as a chromatin modifier in AR regulation. However, the ability of ARIP4 to activate AR function is abolished with mutation in six potential SUMO (small ubiquitin-related modifier) attachment sites [23]. Other chromatin modifications may take place by sumoylation or binding of cofactors. For example, the chromatin remodeling factor Mi-2 $\alpha$  interacts with human c-Myb and activates the transcription of hematopoietic genes [24].

### Corepressors and Their Mechanism of Action

As compared to coactivators, relatively less is known about corepressors (table 2). A true corepressor contains autonomous repression domain and directly interacts with the receptor. It also interacts with components of the transcription machinery and represses the transcription of a specific gene. The repression of transcription may be due to competition among molecules which bind to DNA or may be due to direct silencing of the basal transcription machinery [25]. Thus, a particular gene may be repressed through the recruitment of corepressor molecules to the gene and protein-protein interaction. TR-mediated repression is reversed by cotransfection with either the unliganded retinoic acid receptor (RAR) or C-terminus of the oncoprotein (v-ErbA) [26].

The corepressors are associated with nuclear hormone receptors and recruit histone deacetylase (HDAC)3 and other isoforms that mediate histone deacetylation [27]. Another interacting protein, ZNF366, acts directly or through ER $\alpha$  corepressors, namely RIP140 and CtBP, and inhibits the expression of estrogen-responsive genes by HDAC activity [28]. These findings strongly support the hypothesis that gene transcription is repressed through nucleosomal condensation caused by deacetylation of histones [29].

Both corepressors NCoR and SMRT exist in large protein complexes with estimated sizes of 1.5–2 MDa in HeLa nuclear extracts. Using conventional and immuno-affinity chromatography, HDAC3, transducin ( $\beta$ )-like 1 and a WD-40 repeat-containing protein have been isolated as subunits of the purified SMRT complex. The

HDAC3-containing SMRT and NCoR complexes can bind to unliganded thyroid hormone receptors (TRs) in vitro. The injection of antibodies against HDAC3 or SMRT/NCoR into *Xenopus* oocytes leads to partial relief of repression by unliganded TR/RXR, suggesting both NCoR and SMRT as partner of HDAC-containing complexes and their function in transcriptional repression [30].

### Coregulators and Diseases

Steroid receptors in combination with their coactivators and corepressors mediate precise gene regulation ranging from the ligand-induced transcriptional activation to repression. As studies continue to unfold the role of coregulators in transcriptional regulation by nuclear steroid receptors, it is becoming evident that they are important for understanding the etiology of a variety of diseases such as obesity, diabetes, atherosclerosis, osteoporosis, cancer, neurodegenerative disorders, etc. The coregulators may also be used as therapeutic targets in steroid-related diseases. For example, breast cancer patients show resistance to anticancer drugs, and the majority of them eventually do not respond to tamoxifen therapy [31].

### Coactivators and Diseases

Mutations in CBP coactivator are involved in embryogenesis and chromosomal translocation of p300 gene that causes Rubinstein-Taybi syndrome. The loss of one functional copy of the CBP gene leads to the developmental abnormalities in Rubinstein-Taybi syndrome and possibly the propensity for malignancy [32]. It also causes open neural tube and heart defects in humans, as well as embryonic lethality in mice [33, 34]. The activity of CBP/p300 is also inhibited in neurodegenerative diseases [35].

Coactivators like Ciz1 and FHL2 (four and half LIM domain) interact with ER $\alpha$  and are involved in ovarian and breast cancers [36, 37]. The peroxisome proliferator-activated receptor (PPAR) $\gamma$  coactivator-1 of the PGC-1 gene family regulates lipid and carbohydrate metabolism and inflammation [38]. Knockout studies reveal the effects of two members of the p160 family on energy homeostasis. TIF2 $^{-/-}$  mice are protected against obesity and display enhanced adaptive thermogenesis, whereas SRC1 $^{-/-}$  mice are prone to obesity due to reduced energy expenditure [39]. In addition, TRAP220 knockout re-

veals an early gestational stage with heart failure and exhibits impaired neuronal development with extensive apoptosis [40].

Mutations in receptor gene also inhibit the binding of coactivators and lead to diseases. For example, androgen-insensitive syndrome is developed due to mutation in the DNA-binding domain of AR which prevents interaction of coactivators to the AF-1 region and transmission of activation signal [41]. This syndrome shows various degrees of impairment in the genital virilization [42, 43]. The transcriptional response to AR coactivator (ART-27) is increased by the majority of naturally occurring AR mutations in prostate cancer, but decreased by P340L mutation and androgen-insensitive syndrome [44].

### Corepressors and Diseases

Mutation in the corepressor or change in its interaction with the basal transcription machinery may lead to diseases. For example, mutations in MeCP-2, RB and DAX-1 result in the loss of corepressor interaction leading to embryonic diseases during development [45, 46]. Mutation in MeCP-2, which affects either the methyl-binding domain or the transrepressor domain by deacetylation, causes an X-linked neurodegenerative developmental disorder, Rett syndrome [47]. These mutations result in the loss of recruitment of the SIN3 corepressor to target genes [48]. Mutations in MTA (metastasis-associated protein) 2 are responsible for estrogen-responsive cancer [49]. An ER $\beta$ -associated corepressor NM23-H2 has been identified in the arteries from young subjects ( $27 \pm 6$  years) with benign intimal hyperplasia. The expression of NM23-H2 decreases with the advancement of atherosclerosis and inflammation in human [50].

Mutations in receptors also affect their interaction with corepressors and lead to a number of diseases. For example, acute myelogenous leukemia (AML), which results from translocations involving fusion of DBD of AML protein to the transcriptional repressor ETO/MTG8, is associated with aberrant interaction of corepressor with transcription factors [51]. Similarly, B-cell acute lymphoblastic leukemia involves the chromosomal translocation, which results in the fusion of repression domain of the Ets leukemia protein TEL to the large form of AML. In both cases, corepression arises from the recruitment of NCoR and SIN3-HDAC complex by ETO and TEL [52].



## Therapeutic Approach

The synthetic compounds, which target HAT/HDAC complex or the receptor itself, are used in the therapy of diseases caused by defects in the binding of coregulators.

### *Targeting HAT/HDAC Complex*

The reduction in HDAC activity and HDAC2 expression causes chronic obstructive pulmonary disease which may account for the amplified inflammation and resistance to the actions of corticosteroids. The reduction in HDAC2 expression may be secondary to the oxidative and nitrative stress as a result of cigarette smoking and severe inflammation. It occurs to different degrees in severe asthma, smoking asthmatic patients and cystic fibrosis. Similar mechanisms may also account for the steroid resistance seen in latent adenovirus infections. The reduction in HDAC activity induced by oxidative stress can be restored by theophylline, which acts through specific kinases and reverses steroid resistance in chronic obstructive pulmonary disease and other inflammatory lung diseases [53]. Several histone deacetylase inhibitors have been shown to inhibit tumor growth and now used in clinical trials for the treatment of cancer [54, 55]. The inhibition of HDAC1 by phenylbutyrate also reverses the ETO-mediated transcriptional repression and induces partial differentiation of AML-ETO cell line [56].

### *Targeting Receptors and Binding Partners*

LXRs (LXR $\alpha$  and LXR $\beta$ ) have a sterol-responsive property and can bind directly with several oxysterol metabolites. They are involved in cholesterol transport, glucose metabolism and inflammation. Thus, synthetic LXR ligands have been designed to treat disorders such as atherosclerosis and diabetes [57]. Further, statins modulate the sterol-responsive element-binding protein, which targets genes that are involved in cholesterol and fatty acid metabolism, namely hydroxyl-methyl-glutaryl acetyl Co-enzyme-A (HMG-CoA) reductase, HMG-CoA synthase

and the low-density lipoprotein receptor [58]. Similarly, insulin-like drugs target the PPAR $\gamma$ , whereas several anti-inflammatory drugs inhibit activation of nuclear factor- $\kappa$ B [59].

## Conclusion

The expanding number of coregulators has increased the challenge and added the complexity to understanding the transcriptional regulation of steroid hormone action. One of the future challenges is to determine the specificity of coregulators. For example, the central nervous system is regulated by an array of NR coactivators such as p160/SRC family members, CBP/p300, BRG1, TRAP220 and PGC-1 $\alpha$  as well as corepressors like NCoR and SMRT. In recent years, the study of corepressor biology has become an area of active research. This has led to substantial progress in the identification of a number of novel corepressors with critical roles in determining the action of NR. Emerging data re-emphasize that the regulation of NR by corepressor is as significant as that by coactivator. Although much more work remains to be done, we have begun to gain a deeper insight into the transcriptional regulation of steroid receptors, the role played by chromatin modifications, and the contribution of coactivators and corepressors in the development of pathological conditions. Further study of key coregulators in physiologically relevant animal models and human subjects combined with cell culture models will help to elucidate the detailed mechanism of steroid hormone action and develop the therapeutic strategies for the hormone-related diseases.

## Acknowledgements

We acknowledge the financial support from the Indian Council of Medical Research and Department of Biotechnology, Government of India.

## References

- 1 Evans RM, et al: The steroid and thyroid hormone receptor superfamily. *Science* 1988; 240:889–895.
- 2 Kumar R, et al: The clinical relevance of steroid hormone receptor corepressors. *Clin Cancer Res* 2005;8:2822–2830.
- 3 Helmut D, et al: Agonist-antagonist induced coactivator and corepressor interplay on the human androgen receptor. *Mol Cell Endocrinol* 2003;213:79–85.
- 4 McKenna NJ, Malley BWO: Combinatorial control of gene expression by nuclear receptor and coregulators. *Cell* 2002;108:465–474.
- 5 Hong H, et al: GRIP1, a novel mouse protein that serves as a transcriptional coactivator in yeast for the hormone-binding domains of the steroid receptors. *Proc Natl Acad Sci USA* 1996;93:4948–4952.

- 6 Breeden L, Nasmyth K: Similarity between cell cycle genes of budding yeast and fission yeast and the notch gene of *Drosophila*. *Nature* 1987;329:651–654.
- 7 Yoshinaga SK, et al: Roles of SWI1 SWI2, and SWI3 proteins for translational enhancement by steroid receptors. *Science* 1992;258:1598–1604.
- 8 Kwon H, et al: Nucleosome disruption and enhancement of activator binding by a human SWI/SNF complex. *Nature* 1994;370:477–481.
- 9 Chiba H, et al: Two human homologues of *Saccharomyces cerevisiae* SWI2/SNF2 and *Drosophila* Brahma are transcriptional coactivators cooperating with the estrogen receptor and the retinoic acid receptor. *Nucl Acid Res* 1994;10:1815–1820.
- 10 Peterson CL, et al: Five SWI/SNF gene products are components of a large multisubunit complex required for transcriptional enhancement. *Proc Natl Acad Sci USA* 1994;8:2905–2908.
- 11 Candau R, et al: Histone acetyltransferase activity and interaction with ADA2 are critical for GCN5 function in vivo. *EMBO J* 1997;16:555–565.
- 12 Ogryzko VV, et al: The transcriptional coactivators p<sup>300</sup> and CBP are histone acetyltransferase. *Cell* 1996;87:953–959.
- 13 Onate SA, et al: Sequence and characterization of a coactivator for the steroid receptor superfamily. *Science* 1995;270:1354–1357.
- 14 Kalkhoven E, et al: Isoforms of steroid receptor coactivator 1 differ in their ability to potentiate transcription by the oestrogen receptor. *EMBO J* 1998;17:232–243.
- 15 McNerney EM, et al: Analysis of estrogen receptor transcriptional enhancement by a nuclear hormone receptor. *Proc Natl Acad Sci USA* 1996;93:10069–10073.
- 16 Rachez C, Freedman LP: Mechanisms of gene regulation by vitamin D<sub>3</sub> receptor: a network of coactivator interactions. *Gene* 2000;246:9–21.
- 17 Hirochika K, et al: The chromatin remodeling complex WINAC targets a nuclear receptor to promoters and is impaired in Williams syndrome. *Cell* 2003;113:905–917.
- 18 Janknecht R: The versatile functions of the transcriptional coactivators p300 and CBP and their roles in disease. *Histol Histopathol* 2002;17:657–668.
- 19 Yeung PL, et al: Nuclear localization of coactivator RAC3 is mediated by a bipartite NLS and importin  $\alpha$ 3. *Biochem Biophys Res Commun* 2006;1:13–24.
- 20 Balmer NN, et al: Steroid receptor coactivator AIB1 in endometrial carcinoma, hyperplasia and normal endometrium: correlation with clinicopathologic parameters and biomarkers. *Mod Pathol* 2006;12:1593–1605.
- 21 Leader JE, et al: Epigenetics and the estrogen receptor. *Ann NY Acad Sci* 2006;1089:73–87.
- 22 Bertolotti A, et al: hTAF(II)68, a novel RNA/ssDNA-binding protein with homology to the pro-oncoproteins TLS/FUS and EWS is associated with both TFIID and RNA polymerase II. *EMBO J* 1996;18:5022–5031.
- 23 Domanskyi A, et al: Biochemical characterization of androgen receptor-interacting protein 4. *Biochem J* 2006;3:789–795.
- 24 Saether T, et al: The chromatin remodeling factor Mi-2 $\alpha$  acts as a novel co-activator for human c-Myb. *J Biol Chem* 2007;282:13994–14005.
- 25 Horwitz KB, et al: Nuclear receptor coactivators and corepressors. *Mol Endocrinol* 1996;10:1167–1177.
- 26 Baniahmad A, et al: A transferable silencing domain is present in the thyroid hormone receptor, in the v-erbA oncogene product and in the retinoic acid receptor. *EMBO J* 1992;11:1015–1023.
- 27 Takahiro I, Lazar MA: The NCoR/histone deacetylase 3 complex is required for repression by thyroid hormone receptor. *Mol Cell Biol* 2003;23:5122–5131.
- 28 Lopez-Garcia J, et al: ZNF366 is an estrogen receptor corepressor that acts through CtBP and histone deacetylases. *Nucleic Acid Res* 2006;21:6126–6136.
- 29 Wolffe AP, Pruss D: Targeting chromatin disruption: transcription regulators that acetylate histones. *Cell* 1996;84:817–819.
- 30 Li J, et al: Both corepressor proteins SMRT and NCoR exist in large protein complexes containing HDAC3. *EMBO J* 2000;19:4342–4350.
- 31 Wang LH, et al: Disruption of estrogen receptor DNA-binding domain and related intramolecular communication restores tamoxifen sensitivity in resistant breast cancer. *Cancer Cell* 2006;6:4874–4899.
- 32 Fred P, et al: Rubinstein-Taybi syndrome caused by mutations in the transcriptional coactivator CBP. *Nature* 2002;376:348–351.
- 33 Yao TP, et al: Gene dosage-dependent embryonic development and proliferation defects in mice lacking the transcriptional integrator p300. *Cell* 1998;93:361–372.
- 34 Kung AL, et al: Gene dose-dependent control of hematopoiesis and hematologic tumor suppression by CBP. *Gen Dev* 2000;14:272–277.
- 35 Neri C: New light on polyglutamine neurodegenerative disorders: inference with transcription. *Trend Mol Med* 2001;7:283–284.
- 36 Kobayashi S, et al: FHL2, UBC9 and PIAS1 are novel estrogen receptor  $\alpha$ -interacting proteins. *Endocr Res* 2004;4:617–621.
- 37 Den Hollander P, et al: Ciz1, a novel DNA-binding coactivator of the estrogen receptor  $\alpha$  confers hypersensitivity to estrogen action. *Cancer Res* 2006;22:11021–11029.
- 38 Glass CK: Going nuclear in metabolic and cardiovascular disease. *J Clin Invest* 2006;3:556–560.
- 39 Frederic P, et al: SRC-1 and TIF2 control energy balance white and brown adipose tissues. *Cell* 2002;111:931–941.
- 40 Ito M, et al: Involvement of the TRAP220 component of the TRAP/SMCC coactivator complex in embryonic development and thyroid hormone action. *Mol Cell* 2000;5:683–693.
- 41 Imasaki K, et al: Androgen insensitivity syndrome due to new mutations in the DNA-binding domain of the androgen receptor. *Mol Cell Endocrinol* 1996;120:15–24.
- 42 Eli YA, Jon DH: Single-gene mutations resulting in reproductive dysfunction in women. *N Engl J Med* 1999;340:709–718.
- 43 Zoppi S, et al: Complete testicular feminization caused by amino-terminal truncation of the androgen receptor with downstream initiation. *J Clin Invest* 1993;91:1105–1112.
- 44 Li W, et al: Androgen receptor mutations identified in prostate cancer and androgen insensitivity syndrome display aberrant ART-27 coactivator function. *Mol Endocrinol* 2005;9:2273–2282.
- 45 Nan X, et al: Transcriptional repressions by methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature* 1998;393:386–389.
- 46 Batsche E, et al: Rb enhances p160/SRC coactivator-dependent activity of nuclear receptors and hormone responsiveness. *J Biol Chem* 2005;280:19746–19756.
- 47 Kouzarides T: Histone acetylases and deacetylases in cell proliferation. *Curr Opin Gen Dev* 1999;9:140–148.
- 48 Wong CW, Privalsky ML: Transcriptional repression by the SMRT-mSin3 corepressor: multiple interactions, multiple mechanisms, and a potential role for TFIIB. *Mol Cell Biol* 1998;18:5500–5510.
- 49 Cui Y, et al: Metastasis-associated protein 2 is a repressor of estrogen receptor  $\alpha$  whose overexpression leads to estrogen-independent growth of human breast cancer cells. *Mol Endocrinol* 2006;9:2020–2035.
- 50 Rayner K, et al: NM23-H2, an estrogen receptor  $\beta$ -associated protein, shows diminished expression with progression of atherosclerosis. *Am J Physiol* 2007;292:R743–R750.
- 51 Fenrick R, et al: Both TEL and AML-1 contribute repression domains to the t(12;21) fusion protein. *Mol Cell Biol* 1999;10:6566–6574.
- 52 Lutterbach B, et al: A target of t(8;21) in acute leukemia interacts with the NCoR and mSin3 corepressors. *Mol Cell Biol* 1988;18:7176–7184.
- 53 Adcock IM, et al: Histone deacetylation: an important mechanism in inflammatory lung diseases. *J Chron Obstruct Pulmon Dis* 2005;4:445–455.
- 54 Secrist JP, et al: HDAC inhibitors for the treatment of cancer. *Curr Opin Invest Drugs* 2003;4:1422–1427.
- 55 Bicaku E, et al: Selective inhibition of histone deacetylase 2 silences progesterone receptor-mediated signaling. *Cancer Res* 2008;68:1513–1519.
- 56 Wang J, et al: Inhibitors of histone deacetylase relieve ETO-mediated repression and induce differentiation of AML1-ETO leukemia cells. *Cancer Res* 1999;12:2766–2769.
- 57 Michael LF, et al: The pharmacology of LXRs. *Med Chem* 2005;8:729–740.
- 58 De Nigris F, et al: Coregulators new insights in the transcriptional activity and coregulator molecules in the arterial wall. *Int J Cardiol* 2002;2–3:153–168.
- 59 Tanaka T, et al: Ligands for peroxisome proliferator-activated receptors and inhibit chemically induced colitis and formation of aberrant crypt foci in rats. *Cancer Res* 2001;61:2424–2428.