View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Factors that Mediate and Modulate Androgen Action

M. J. McPhaul
Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Texas Southwestern Medical Center, Dallas, TX USA

Androgens mediate a wide range of processes during embryogenesis and in the adult. In mammals, although a number of steroids can be shown to exert androgenic effects using *in vitro* and *in vivo* assays, testosterone and its 5α reduced metabolite, 5α-dihydrotestosterone (DHT) are considered to represent the principal physiologic androgens. Furthermore, although the effects that androgens exert differ widely among different tissues and cell types, genetic and biochemical data suggest that these effects are mediated via the protein products of a single androgen receptor gene, which is encoded on the X-chromosome in mammals. ***Key words: Androgen receptor, expression, eukaryotes. JID Symposium Proceedings 8:1–5, 2003***

The last decade has witnessed an explosion of information regarding the manner in which steroid hormones modulate gene expression. At present, a body of increasingly detailed information is available concerning the mechanisms by which nuclear receptors, such as the androgen receptor, regulate the activity of target genes. Such experiments have identified a host of molecules capable of modulating the activation or repression of genes by members of the nuclear receptor family. In parallel to experiments focused on the mechanisms by which nuclear receptors regulate the transcription of responsive genes, other experiments have demonstrated the importance of androgen metabolism in specific cell types.

The results of such investigations provide a framework in which to view the mechanisms by which genes are regulated differentially by androgens in different tissues and in different cell types. The contribution of these influences to the regulation of genes by androgens in normal physiology and in disease states is in only its earliest stages.

STRUCTURE OF THE ANDROGEN RECEPTOR (AR)

The cloning of the androgen receptor (AR) revealed it to be a member of a large gene family, the nuclear receptor family. Inspection of the predicted amino acid sequence of the AR demonstrates that in common with other members of the nuclear receptor family, the AR protein sequence contains highly conserved DNA-binding and ligand-binding domains (Evans, 1988). These modular domains mediate the recognition of target DNA sequences by the receptor and the high affinity binding of its androgenic ligands (Fig. 1).

Comparison of the predicted amino acid sequences of the AR to other members of the NR family demonstrate that the AR is most closely related to the progesterone and mineralocorticoid receptors. The androgen receptor is one of the largest members of the nuclear receptor family, owing to its large amino terminal segment. This region, which is critical for maximal transcriptional activation of responsive genes, contains a number of repeated amino acid motifs. Alteration in the size of the glutamine repeat element has been linked to the pathogenesis of X-linked Spinal and Bulbar Muscular Atrophy (SBMA), to an increased frequency of developing aggressive forms of prostate cancer, and to a tendency to display oligoazospermia (McPhaul, 2000).

The structure of the AR was determined by the cloning of cDNAs encoding the receptor protein. Subsequent experiments identified a second form of the AR, termed AR-A. On the basis of experiments using epitope specific antibodies, the AR-A isoform is believed to be identical to the long version of the androgen receptor (AR-B) in most of its predicted amino acid sequence, but lacks the first 187 amino acids (Zoppi *et al*, 1993; Wilson and McPhaul, 1994). Cell transfection assays have demonstrated measurable differences in the activities of these isoforms when assayed using different reporter genes and in different cell types (Gao and McPhaul, 1998). Despite striking similarities to the A- and B- forms of the progesterone receptor, an immunoblot survey examining the abundance of the AR-A isoform in cells and tissues suggest that it is expressed at low levels (Wilson and McPhaul, 1996). This AR-A isoform is believed to be derived from internal translational initiation, and not by translation of a separate AR-A mRNA transcript (**Fig 1**).

COACTIVATORS

The availability of model reporter genes permitted the functional characterization of many members of the nuclear receptor family. The results of transfection assays of receptor function suggested that intermediary factors played an important role in the normal function of members of the NR family. Investigations in a number of laboratories sought to identify these factors using biochemical and genetic methods. The first of these factors, SRC 1, was identified as a protein that interacted with the ligand-binding domain of the progesterone receptor in a ligand dependent fashion (Oñate *et al*, 1995). In transfection assays, SRC 1 was shown to be capable of augmenting the function of the progesterone receptor when activated by a progesterone receptor agonist. Subsequent investigations focused on the mechanism of action of

Accepted for publication February 1, 2003
Reprint requests to: Michael J. McPhaul, M.D., Department of Internal Medicine, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8857 USA, Email: Michael.McPhaul@utsouthwestern.edu
Abbreviations: AR, androgen receptor; 5α-dihydrotestosterone, DHT; NR, nuclear receptor; T, Testosterone.

0022-202X/03/$15.00 · Copyright © 2003 by The Society for Investigative Dermatology, Inc.

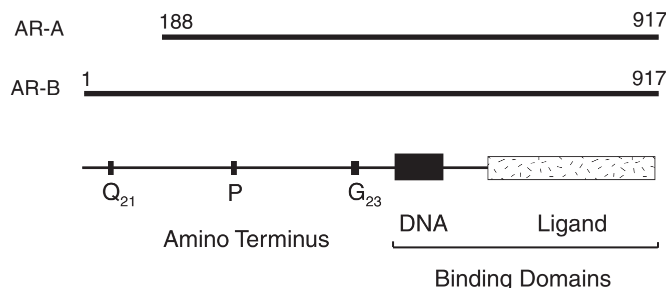

Figure 1. Schematic of the structure of the human androgen receptor. The DNA and ligand binding domains of the receptor are shown as boxes. These critical domains comprise most of the carboxyl terminal portion of the receptor. The amino terminal portion of the AR is required for full transcriptional activation of responsive genes. Elements containing stretches of repeated amino acid residues [glutamine (Q), proline (P), and glycine (G)] are found with in this amino terminal segment. The glutamine and glycine repeats have been demonstrated to be polymorphic in groups of normal individuals.

other nuclear receptors, particularly the glucocorticoid and estrogen receptors, have identified other related members of this gene family, now termed the P160 or SRC family of nuclear coactivators (Leo and Chen, 2000). These proteins are believed to augment the transcriptional activity of nuclear receptors by recruiting enzymatic activities important to the remodeling of chromatin and by stabilizing the transcriptional preinitiation complex (McKenna *et al*, 1999; Zoppi *et al*, 2002).

A great deal of information has been published relating to the identification of proteins that interact with different members of the NR family, including the AR. Such studies have demonstrated that receptor function can be modulated differentially in different cellular contexts. Despite the conceptual importance of such experiments, there is much less information tying these cell-based results to physiologically relevant processes. The results of experiments in which individual SRC members have been disrupted have suggested that considerable redundancy exists in the actions of these proteins. The phenotypes have been relatively subtle when only individual members are disrupted (Xu *et al*, 1998; Weiss *et al*, 1999). Only when multiple members of this family are disrupted do more severe phenotypes emerge.

COREPRESSORS

Experiments examining the behavior of genes regulated by thyroid and retinoic acid receptors demonstrated that these receptors exerted two distinct effects on gene activity. In addition to the stimulation of gene activity that occurred when an agonist ligand was added, it was noted that expression of the TR (or RAR) in cells led to a decrease in the basal activity of model responsive reporter genes. Experiments using fusion proteins containing portions of the TR and RAR demonstrated that this capacity to inhibit gene activity could be localized to small segments of these receptors. Extrapolation of these findings using genetic and biochemical methods led to the identification of two proteins, SMRT (silencing mediator of the retinoid and thyroid hormone receptors (Chen and Evans, 1995)) and NCoR (nuclear receptor corepressor (Horlein *et al*, 1995)) that were responsible for these inhibitory effects on gene expression. The predicted amino sequences of SMRT and NCoR reveal them to be large proteins ($>$2440 amino acids in length) that contain similar structural motifs. Subsequent experiments have demonstrated that each protein is modular and contains regions responsible for mediating the interaction with nuclear receptors (Hu and Lazar, 1999; Nagy *et al*, 1999) and for the assembly of protein complexes that mediate repression (repression domains).

The mechanisms by which the repressive effects on gene transcription are exerted have been shown to be the result of the recruitment of protein complexes that contain proteins that possess enzymatic activities, such as histone deacetylase activities (HDACs) (Perissi *et al*, 1999; Jepsen *et al*, 2000). The enzymatic activities are believed to facilitate the assembly of compact or inactive chromatin structures. Important for the understanding the action of antagonists of steroid receptor function, subsequent studies have demonstrated that SMRT and NCoR are important modulators of the effects of steroid receptor antagonists (Smith *et al*, 1997; Jackson *et al*, 1997). In these experiments, it has been shown that corepressor levels in cells can alter the levels of repression that are observed (Soderstrom *et al*, 1997).

STABLE COMPLEXES AND NR FUNCTION

The coactivators and corepressors described above have been identified on the basis of affinity and interaction with members of the nuclear receptor family using yeast two-hybrid assays or physical methods. Using different methodologies other investigators have examined the association of members of the nuclear receptor family with stable complexes present in the nuclear compartment of mammalian cells. Such studies led to the identification of the TRAP and DRIP complexes that associate with the thyroid hormone receptor and vitamin D receptor, respectively (Fondell *et al*, 1996; Rachez *et al*, 1999). These large, macromolecular complexes are composed of multiple distinct polypeptides. Surprisingly, analysis of the composition of these complexes revealed that in many instances composition was distinct and did not contain proteins identified as coactivators or corepressors in biochemical or yeast screening assays (described above). Instead, these complexes were found to contain components in common with other macromolecular complexes identified as important to the transcription of many the broad classes of genes in yeast and in mammalian cells (Myers and Kornberg, 2000). These observations suggest that distinct classes of proteins either participate in the regulation of different classes of responsive genes or play roles that are temporally distinct. Recent studies from the laboratory of Myles Brown suggest a complex and dynamic interaction between these different groups of proteins (Shang *et al*, 2000).

CONFORMATIONAL CHANGES AND ANDROGEN RECEPTOR FUNCTION

The activity of the AR (and other members of the NR family) can be regulated by agonist and antagonist ligands. An increasing body of detailed information is becoming available concerning how different classes of ligands have distinct effects on receptor function. These studies have employed crystallography to define the conformational changes that occur as a result of binding of agonistic or antagonistic ligands to their respective receptors. They indicate that binding of agonist ligands causes the NR to assume an activated conformation in which selected surfaces are exposed, permitting coactivators that modulate gene activation to bind. By contrast, the binding of antagonist ligands to an NR causes the receptor to assume a different conformation in which the surfaces necessary for coactivator binding are no longer exposed. It is believed that these conformational changes underlie the selective recruitment of coactivators or corepressors to ligand-bound nuclear receptors and contribute to the differential effects of individual ligands as agonists or antagonists (Brzozowski *et al*, 1997).

Although this description might suggest that such conformational changes might be agonist or antagonist in nature, other experiments suggested that these conformations are dynamic and that multiple different conformations of a nuclear receptor may result from the binding of different ligands (Paige *et al*, 1999) and may affect the extent that coactivator and/or corepressors are

recruited. While additional explanations are certainly possible, these changes may well contribute to the differing degrees of agonism or antagonism that are observed in some tissues following administration of tissue-selective modulators of steroid receptor functions, such as the selective estrogen receptor modulators (SERMs).

TESTOSTERONE AND DIHYDROTESTOSTERONE

The importance of 5α-dihydrotestosterone (DHT) formation in androgen target tissues was first suggested by independent experiments in the laboratories of Liao and Wilson. These investigators demonstrated that following the administration of radiolabeled T to animals, T was converted enzymatically and that labeled DHT was found bound to the androgen receptor in the nuclei of cells in androgen target tissues, such as the prostate (Anderson and Liao, 1968; Bruchovsky and Wilson, 1968).

Testosterone and 5α- dihydrotestosterone are the principal androgens in mammals. Although these molecules differ only in the presence of a single double bond between carbons 4 and 5 of the A ring of the steroid nucleus, physiological and genetic data demonstrate that the two hormones are not biologically equivalent (**Fig 2**). Patients with genetic 5α-reductase deficiency are 46, XY male pseudohermaphrodites. These individuals demonstrate normal testicular differentiation and normal levels of circulating testosterone, yet display defects of male phenotypic development and display female psychosocial development. In animal experiments, the administration of 5α-reductase inhibitors during embryogenesis impairs or abolishes development of the prostate. When administered to post pubertal animals, 5α-reductase inhibitors cause a partial involution of the prostate and a reduction in the levels of expression of androgen-regulated genes.

Attempts to purify 5α-reductase activities were not successful. Ultimately, the nature of these enzymes awaited studies in which cDNAs encoding the enzymes were isolated by expression cloning by Andersson and colleagues (Andersson *et al*, 1989). Using these techniques, they identified cDNAs encoding 2 distinct 5α-reductase isozymes in rat and humans. Subsequent experiments have demonstrated that this dichotomy is present in many other mammalian species (Russell and Wilson, 1994). Although the role of the 5α-reductase I enzyme in human physiology remains uncertain, the 5α-reductase II enzyme is defective in patients with the 5α-reductase deficiency, is crucial for prostate formation and development, and has been implicated in the pathogenesis of male pattern baldness (Wilson *et al*, 1993).

How do the actions of T and DHT differ? Any number of potential explanations might account for the observed differences in the biological actions of T and DHT. Such differences might reflect subtle differences in the conformation of the AR when complexed to T, compared to DHT. Such differences might result in the recruitment of different sets of coactivators causing the activation of related, overlapping sets of genes. At the other extreme, these differences might reflect other influences, such as differential metabolism of the two steroid hormones.

Investigations of this type have been conducted using whole cell and broken cell binding assays to examine the manner that these two androgens are bound by the androgen receptor. These studies have demonstrated that although T and DHT are both bound with high affinity by the AR, 5α-dihydrotestosterone is bound several fold more avidly than is T. When experiments are performed to examine the stability of preformed complexes of the AR with T and DHT, AR-DHT complexes are found to be more stable and dissociate less rapidly (Grino *et al*, 1990). Such findings suggest that differences in the rate of binding and dissociation of T and DHT are likely to contribute to the differential regulation of genes by these two androgens.

This model has been examined formally in only a limited number of models in a limited number of systems. In transfection experiments, activity of the model androgen-responsive reporter gene MMTV-CAT was examined following stimulation with differing concentrations of T and DHT. These experiments demonstrated that the kinetics of induction of the reporter gene by T and DHT differed at low concentrations, but that the maximum activation achieved by both hormones was identical. Importantly, these experiments were conducted in cells that were very inactive in the metabolism of androgen (Deslypere *et al*, 1992).

Experiments examining these mechanisms in intact animal models are even more limited. Avila and coworkers prepared RNA from prostate tissue isolated from three groups of rats: intact, castrate, and intact animals treated with Finasteride (a 5α-reductase inhibitor) (Avila *et al*, 1998). Genes that displayed patterns of expression suggesting differential regulation under these three conditions identified using differential display PCR. In these experiments, the patterns of gene expression observed for many genes were felt to be consistent with the "signal amplification" model, as was observed for the MMTV-CAT. In a small proportion of instances, the patterns of gene expression could not be easily explained on the basis of kinetic differences of binding of T and DHT to the receptor. These results, instead, suggested that the changes may instead reflect the formation of complexes with distinct conformations (in response to the binding of T or DHT). Alternatively, these changes might reflect the regulation of genes selectively via an indirect mechanism (e.g., by the formation of estrogen from T, a conversion that is impossible for DHT).

From the body of available information, a model has emerged in which the differential effects of T and DHT reflect (1) the different affinity with which T and DHT are bound; and (2) the measurable differences in the stabilities of the DHT-AR and

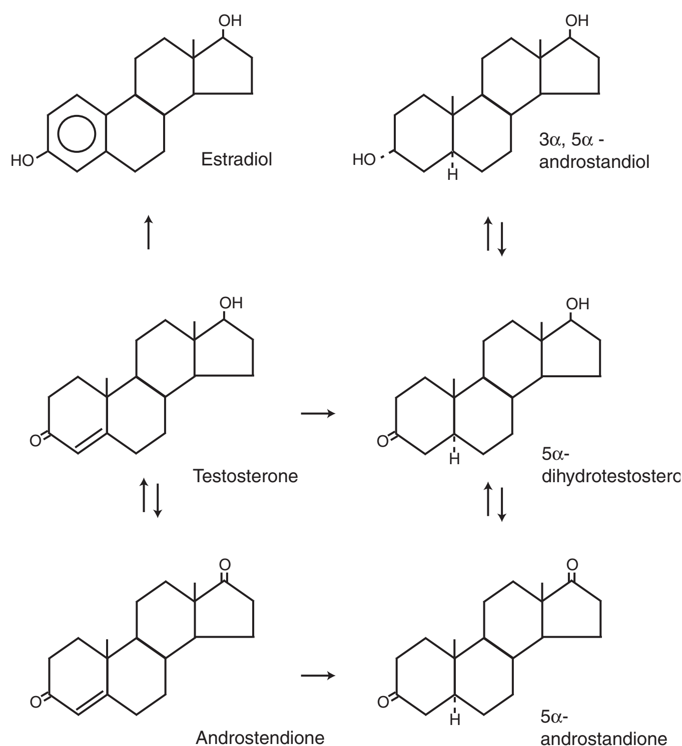

Figure 2. Metabolic interconversions of androgens testosterone can be converted irreversibly (*single arrows*) to compounds with distinctly different biological activities. 5α-reduction of testosterone to 5α-dihydrotestosterone by steroid 5α-reductase increases the potency of testosterone in many biological systems. Aromatization by the cytochrome p450 aromatase converts the potent androgen testosterone into the potent estrogen estradiol. In addition to these irreversible conversions, other reversible pathways (*bi-directional arrows*) are believed to modulate the levels of androgen in target cells.

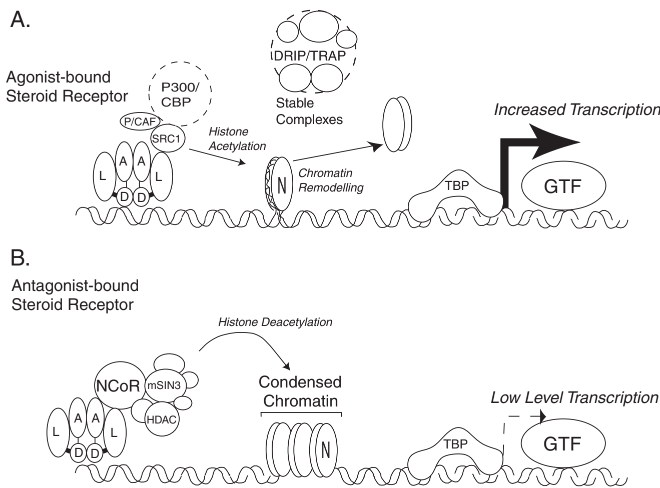

Figure 3. Nuclear receptors recruit distinctive complexes to the sites of transcriptional initiation of genes that hormonally responsive. A general model for the activities of coactivators and corepressors in the modulation of the transcription of responsive genes by nuclear receptors is depicted using steroid receptors as representative members of this family. (*A*) The binding of an agonist bound steroid receptor to specific sequences adjacent to the site of transcription initiation of a responsive gene recruits coactivator complexes containing proteins such as SRC-1, p300/CBP, and DRIPs/TRAPs. Enzymatic activities contained within these complexes (e.g., histone acetyl transferase) modify the local chromatin structure. In some instances, these modifications may result in large-scale alterations of chromatin organization. These changes make the transcription unit more accessible to the assembly and stability of transcription initiation complexes and results in an increase in the rate of transcription. Experiments analyzing the composition of complexes at the sites of transcription initiation have demonstrated that the assembly and disassembly of such complexes is dynamic (Shang *et al*, 2000) (*B*) The binding of an antagonist to nuclear receptors results in the recruitment of protein complexes containing corepressors such as NCoR and SMRT. The enzymatic activities (e.g. deacetylases) associated with these corepressor complexes, which include SIN3 and HDACs, leads to a condensation of chromatin structure and a decreased level of gene transcription. (A: amino terminus of NR with activation functions; D: DNA binding domain of NR; L: ligand binding domain of NR; N: nucleosome; TBP: TATA binding protein; GTF: general transcription factors.)

T-AR complexes. This model presupposes that the concentrations of androgen in target cells is limiting in those tissues in which differential regulation of genes by T and DHT is observed. While this hypothesis is adequate to explain the patterns of expression of most androgen-responsive genes, exceptions have been identified. In these instances, additional influences may be involved. In some instances such differences may derives from metabolic conversions that are specific for each ligand (e.g., DHT is nonaromatizable). Differential coactivator recruitment by the T-AR or DHT-AR remains a theoretical possibility (**Figs 2 and 3**).

ADDITIONAL MODIFIERS OF ANDROGEN ACTION

Much of the preceding has focused on how factors identified to regulate the activity of different NR family members can serve to modulate the function of the AR. Specifically, this discussion has focused on the roles played by NR coactivators and repressors, and the differential action and synthesis of T and DHT in the modulation of AR-responsive genes.

Many tissues and cell types actively metabolize the physiologic ligands, T and DHT. One of the most important contributors to this metabolism is the 17-hydroxysteroid dehydrogenase family (17-HSD) (Peltoketo *et al*, 1999). These enzymes catalyze the reversible oxidation-reduction of the hydroxyl group present at the 17 positions of many steroids, including androgens. At least eight distinct genes have been described. The patterns of expression vary widely among tissues and even among different cell types of an individual tissue. Such differences may serve to modulate androgen levels – and thus androgen action – between different cell types.

Additional enzymatic conversions may also exert important influences on androgen levels. Selected members of the 3α-HSD family are also capable of catalyzing the formation or inactivation of androgens (Penning, 1999). Enzymes of both types have specific substrate preferences (e.g., androgens, estrogens) and preferentially catalyze oxidative or reductive reactions (**Fig 2**). Activities of this type have been implicated in the development of the male phenotype in the marsupial (Shaw *et al*, 2000), and may prove to play a role in the actions of androgen in mammals as well.

Ligand-independent activation of the progesterone receptor was first described in 1991. In these studies, the chicken PR was shown to be capable of activation, in the absence of ligand, when stimulated by cAMP (Power *et al*, 1991). These observations stimulated investigations in a number of different systems to determine whether other nuclear receptors could also be activated in a ligand-independent fashion. While a number of studies have reported the ligand-independent activity of androgen receptor (Ikonen *et al*, 1994; Nazareth and Weigel, 1996; Darne *et al*, 1998), the relevance of these activities to normal androgen physiology has been demonstrated in only a few model systems (Mani *et al*, 1994).

CONCLUSION

A number of different influences have been identified to contribute to the diversity of androgen action that is observed in different tissues and cell types. The differential expression of coactivators and corepressors, as well as differences in the rates of synthesis and inactivation of active androgens have all been shown to contribute to variations in the actions of androgens in different model systems. The present challenge is to take examine individual systems to assess the contribution of each modifier to the biological system under investigation. Only in this fashion will it be possible to determine the extent to which these same factors participate in the pathogenesis of the skin diseases in which androgens have been implicated.

Grant support: Robert A. Welch Foundation #I-1090, NIH grants #DK03892, DK52678

REFERENCES

Anderson KM, Liao S: Selective retention of dihydrotestosterone by prostatic nuclei. *Nature* 219:277–279, 1968

Andersson S, Bishop RW, Russel DW: Expression cloning and regulation of steroid 5 alpha-reductase, an enzyme essential for male sexual differentiation. *J Biol Chem* 264:16249–16255, 1989

Avila DM, Fuqua SAW, George FW, McPhaul MJ: Identification of genes expressed in the rat prostate that are modulated differently by castration and Finasteride treatment. *J Endocrinol* 159:403–411, 1998

Bruchovsky N, Wilson JD: The conversion of testosterone to 5-alpha-androstan-17-beta-ol-3-one by rat prostate in vivo and in vitro. *J Biol Chem* 243:2012–2021, 1968

Brzozowski AM, Pike AC, Dauter Z, *et al*: Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature* 389:753–758, 1997

Chen JD, Evans RM: A transcriptional co-repressor that interacts with nuclear hormone receptors. *Nature* 377:454–457, 1995

Darne C, Veyssiere G, Jean C: Phorbol ester causes ligand-independent activation of the androgen receptor. *Eur J Biochem* 256:541–549, 1998

Deslypere J-P, Young M, Wilson JD, McPhaul MJ: Testosterone and 5-dihydrotestosterone interact differently with the androgen receptor to enhance transcription of the MMTV-CAT reporter gene. *Mol Cell Endocrinol* 88:15–22, 1992

Evans RM: The steroid and thyroid hormone receptor superfamily. *Science* 240: 889–95, 1988

Fondell JD, Ge H, Roeder RG: Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. *Proc Natl Acad Sci USA* 93:8329–8333, 1996

Gao TS, McPhaul MJ: Functional activities of the A- and B- forms of the human androgen receptor in response to androgen receptor agonists and antagonists. *Mol Endocrinol* 12:654–663, 1998

Grino PB, Griffin JE, Wilson JD: Testosterone at high concentrations interacts with the human androgen receptor similarly to dihydrotestosterone. *Endocrinology* 126:1165–1172, 1990

Horlein AJ, Naar AM, Heinzel T, *et al*: Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. *Nature* 377: 397–404, 1995

Hu X, Lazar MA: The CoRNR motif controls the recruitment of corepressors by nuclear hormone receptors. *Nature* 402:93–96, 1999

Ikonen T, Palvimo JJ, Kallio PJ, Reinikainen P, Janne OA: Stimulation of androgen-regulated transactivation by modulators of protein phosphorylation. *Endocrinology* 135:1359–1366, 1994

Jackson TA, Richer JK, Bain DL, Takimoto GS, Tung L, Horwitz KB: 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, 1997

Jepsen K, Hermanson O, Onami TM, *et al*: Combinatorial roles of the nuclear receptor corepressor in transcription and development. *Cell* 102:753–763, 2000

Leo C, Chen JD: The SRC family of nuclear receptor coactivators. *Gene* 245:1–11, 2000

Mani SK, Allen JM, Clark JH, Blaustein JD, O'Malley BW: Convergent pathways for steroid hormone- and neurotransmitter-induced rat sexual behavior. *Science* 265:1246–1249, 1994

McKenna NJ, Lanz RB, O'Malley BW: Nuclear receptor coregulators cellular and molecular biology. *Endocrine Rev* 20:321–344, 1999

McPhaul MJ: Mutations that alter androgen receptor function. In: DeGroot L, Jameson JL (eds) *Endocrinology*, 4th edn. Philadelphia: W.B. Saunders, 2000:p 2296–2307

Myers LC, Kornberg RD: Mediator of transcriptional regulation. *Annu Rev Biochem* 69:729–749, 2000

Nagy L, Kao HY, Love JD, Li C, Banayo E, Gooch JT, Krishna V, Chatterjee K, Evans RM, Schwabe JW: Mechanism of corepressor binding and release from nuclear hormone receptors. *Genes Dev* 13:3209–3216, 1999

Nazareth LV, Weigel NL: Activation of the human androgen receptor through a protein kinase A signaling pathway. *J Biol Chem* 271:19900–19907, 1996

Onate SA, Tsai SY, Tsai MJ, O'Malley BW: Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* 270:1354–1357, 1995

Paige LA, Christensen DJ, Gron H, *et al*: Estrogen receptor (ER) modulators each induce distinct conformational changes in ER alpha and ER beta. *Proc Natl Acad Sci USA* 96:3999–4004, 1999

Peltoketo H, Luu-The V, Simard J, Adamski J: 17beta-hydroxysteroid dehydrogenase (HSD)/17-ketosteroid reductase (KSR) family; nomenclature and main characteristics of the 17HSD/KSR enzymes. *J Mol Endocrinol* 23:1–11, 1999

Penning TM: Molecular determinants of steroid recognition and catalysis in aldo-keto reductases. Lessons from 3alpha-hydroxysteroid dehydrogenase. *J Steroid Biochem Mol Biol* 69:211–225, 1999

Perissi V, Staszewski LM, McInerney EM, *et al*: Molecular determinants of nuclear receptor–corepressor interaction. *Genes Dev* 13:3198–3208, 1999

Power RF, Mani SK, Codina J, Conneely OM, O'Malley BW: Dopaminergic and ligand-independent activation of steroid hormone receptors. *Science* 254:1636–1639, 1991

Rachez C, Lemon BD, Suldan Z, *et al*: Ligand-dependent transcription activation by nuclear receptors requires the DRIP complex. *Nature* 398:824–828, 1999

Russell DW, Wilson JD: Steroid 5 alpha-reductase: Two genes/two enzymes. *Annu Rev Biochem* 63:25–61, 1994

Shang Y, Hu X, DiRenzo J, Lazar MA, Brown M: Cofactor dynamics and sufficiency in estrogen receptor-regulated transcription. *Cell* 103:843–852, 2000

Shaw G, Renfree MB, Leihy MW, Shackleton CH, Roitman E, Wilson JD: Prostate formation in a marsupial is mediated by the testicular androgen 5 alpha-androstane-3 alpha,17 beta-diol. *Proc Natl Acad Sci USA* 97:12256–12259, 2000

Smith CL, Nawaz Z, O'Malley BW: Coactivator & corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. *Mol Endocrinol* 11:657–666, 1997

Soderstrom M, Vo A, Heinzel T, *et al*: Differential effects of nuclear receptor corepressor (N-CoR) expression levels on retinoic acid receptor-mediated repression support the existence of dynamically regulated corepressor complexes. *Mol Endocrinol* 11:682–692, 1997

Weiss RE, Xu J, Ning G, Pohlenz J, O'Malley BW, Refetoff S: Mice deficient in the steroid receptor co-activator 1 (SRC-1) are resistant to thyroid hormone. *EMBO J* 18:1900–1904, 1999

Wilson JD, Griffin JE, Russell DW: Steroid 5 alpha-reductase 2 deficiency. *Endocr Rev* 14:577–593, 1993

Wilson CM, McPhaul MJ: A and B forms of the androgen receptor are present in human genital skin fibroblasts. *Proc Natl Acad Sci USA* 91:1234–1238, 1994

Wilson CM, McPhaul MJ: A and B forms of the androgen receptor are expressed in a variety of human tissues. *Mol Cell Endocrinol* 120:51–57, 1996

Xu J, Qiu Y, DeMayo FJ, Tsai SY, Tsai MJ, O'Malley BW: Partial hormone resistance in mice with disruption of the steroid receptor coactivator-1 (SRC-1) gene. *Science* 279:1922–1925, 1998

Zoppi S, Wilson CM, Harbison MD, Griffin JE, Wilson JD, McPhaul MJ, Marcelli M: Complete testicular feminization caused by an amino terminal truncation of the androgen receptor with downstream initiation. *J Clin Invest* 91:1105–1112, 1993

Zoppi S, Young M, McPhaul MJ: Regulation of Gene Expression by the Nuclear Receptor Family. In: Mason JI, (ed) *Genetics of Steroid Biosynthesis, Function.* Reading, UK: Harwood Academic Publishers, 2002: pp 376–403