Journal of Cellular Biochemistry Supplements 30/31:185–193 (1998)

# Steroid Receptors at the Nexus of Transcriptional Regulation

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**Abstract** During the past few years, our understanding of nuclear receptor action has dramatically improved as a result of the identification and functional analysis of co-regulators such as factors involved in chromatin remodeling, transcription intermediary factors (co-repressors and co-activators), and direct interactions with the basal transcriptional machinery. Furthermore, the elucidation of the crystal structures of the empty ligand-binding domains of the nuclear receptor and of complexes formed by the nuclear receptor's ligand-binding domain bound to agonists and antagonists has contributed significantly to our understanding of the early events of nuclear receptor action. However, the picture of hormone- and hormone receptor-mediated mechanisms of gene regulation remain incomplete and extremely complicated when one also considers the "nontraditional" interactions of hormone-activated nuclear receptors, for example, interactions between the activated steroid receptors and components of the chromatin/nuclear matrix; and finally the nongenomic effects that steroid hormones can exhibit with other signaling pathways. In this prospectus on steroid receptors, we discuss the implications of various steroid hormone and nuclear receptor interactions and potential future directions of investigation. J. Cell. Biochem. Suppls. 30/31:185–193, 1998. © 1998 Wiley-Liss, Inc.

**Key words:** steroid receptor action; co-repressors; co-activators

In order to further understand steroid hormone/receptor function, we must gain even greater insight into the numerous aspects of nuclear receptor structure, receptor–ligand structure, receptor–protein interactions, and receptor chromatin/nuclear matrix interactions. In this report, we briefly mention several aspects of receptor structure and receptor–protein interactions that are likely to be critical to the function of transcription regulatory complexes. An increasing body of evidence suggests that steroid hormones can also act through "nontraditional" signaling mechanisms; the ramifications of these interactions are just becoming elucidated, so this topic will be briefly touched upon. These topics are all worthy of lengthy review. The brief descriptions presented are meant as an introduction and to point out the complexity of the issues involved before commenting on potential future areas of investigation.

## NUCLEAR RECEPTOR STRUCTURE

Many physiological events, such as development, control of homeostasis, reproduction, inhibition or induction of cellular proliferation, differentiation, and death, are regulated by the actions of small lipophilic hormones acting through nuclear hormone receptors that bind to cognate hormone and function as ligand-regulated transcription factors.

The nuclear receptor superfamily is a group of transcriptional regulatory proteins that share conserved structure and function. The superfamily includes receptors for a variety of lipophilic hormones such as steroids, thyroid hormones, retinoids, and vitamin $D_3$. In general, all members of the nuclear receptor superfamily display a similar structural organization with an N-terminal region A/B, followed by a DNA-binding domain (DBD) consisting of two zinc fingers (region C), a hinge region D, and the hormone-binding domain (HBD) region E/F. The transcriptional activity of the nuclear receptors is mediated by way of two autonomous transactivation functions, a constitutively active activation function (AF)-1 located within

Contract grant sponsor: National Institutes of Health; Contract grant number: HD-07108; Contract grant sponsor: Mayo Foundation.

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Received 9 September 1998; Accepted 10 September 1998

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the A/B region and a ligand-dependent AF-2 arising in the LBD [Hurd and Moudgil, 1998] (Fig. 1).

The nuclear receptors bind DNA as homodimers, such as the progesterone receptor (PR), and/or as heterodimers, for example, the retinoic acid receptor (RAR), thyroid hormone receptor ($T_3R$), and the vitamin $D_3$ receptor (VDR), along with the promiscuous heterodimerization partner, retinoid X receptor (RXR), to cognate hormone response elements (HREs) [Mangelsdorf and Evans 1995]. These specific DNA-binding sites are located in hormone-regulated genes and show twofold rotational symmetry, reflecting the subunit structure of a symmetrical homodimer, or direct repeats with variable spacing between response element half-sites for heterodimers [Gronemeyer and Moras, 1995]. Simply, a stable receptor–DNA interaction and the AF structures mediate interactions directly or through transcriptional intermediary factors (TIFs) with basal transcription factors resulting in enhanced or inhibited initiation of transcription of hormonally regulated genes [Beato and Sanchez-Pacheco, 1996].

## STEROID RECEPTORS INTERACT WITH "MOLECULAR MACHINES" THAT REGULATE THE GENOME

The typical nucleus of a human somatic cell contains approximately 50,000–100,000 genes, encoded by $6 \times 10^9$ base pairs (bp) of DNA at a total length of about 2 m, all of which must fit into the nucleus. The genes are packaged and organized to allow the use of necessary genes and the storage of less important genes. This packaging and organization is achieved by proteins that, together with DNA, form a complex structure referred to as chromatin. The structural unit of chromatin is the nucleosome, which consists of about 146 bp of DNA wrapped around an octamer of four different histone proteins

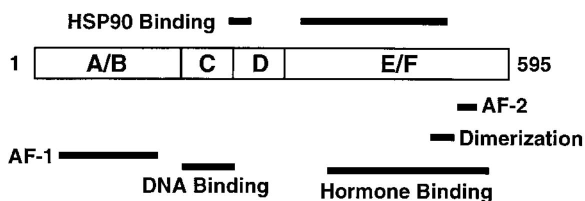


Fig. 1. Primary structure of a steroid receptor. Illustrated are regions A–F with subdomains and their function represented as black lines [Hurd and Moudgil, 1998].

(H2A, H2B, H3, and H4) [Van Holde, 1988]. Post-translational modification of histone proteins has been shown to be an important modulator of the repressive chromatin state through acetylation. Therefore, chromatin organization presents a sizable barrier to the process of RNA transcription, inhibiting both the accessibility of the general transcription machinery to promoter sequences and the binding of upstream regulatory proteins. So, how is the repressive nature of chromatin structure overcome by transcription factors, in particular, the nuclear receptors?

It appears that chromatin structure, whether repressive or conducive to transcription, is maintained by the complex interactions of large multisubunit, energy requiring, protein complexes referred to as molecular machines [Peterson and Tamkun, 1995]. Recent experimental evidence in yeast suggests that a large, well conserved multisubunit protein complex, the switching mating type (SWI) or sucrose nonfermenting (SNF) SWI/SNF complex, uses ATP-hydrolysis to remodel chromatin to drive transcription factors onto nucleosomal transcription factor-binding sites, relaxing chromatin repression, and allowing transcription [Varga-Weisz and Becker, 1998]. The yeast SWI/SNF complex is not abundant and is not essential for viability, whereas the RSC (remodels the structure of chromatin) appears to be more abundant and essential for viability [Gregory and Horz, 1998]. Thus, there appears to be an hierarchy of specialized chromatin modifying protein complexes. The SWI/SNF complex disturbs chromatin structure reversibly, allowing transcription factor access. If the transcription factor does not bind the DNA, the complex reverts to inaccessible chromatin, as characterized by DNase 1 hypersensitivity [Cairns et al., 1996]. So there appears to be a synergism between the remodeling machinery and sequence-specific DNA-binding factors. The direct protein–protein interactions between SWI/SNF and non-nuclear receptor transcription factors have yet to be demonstrated.

However, targeted nucleosome remodeling by SWI/SNF complex has been demonstrated. The activated glucocorticoid receptor (GR) binds to naked DNA with the same affinity as nucleosomal DNA. Moreover, GR does not disrupt nucleosomal DNA. In the presence of mammalian SWI/SNF complex, in vitro GR bound to DNA resulted in nucleosomal disruption

[Oestlund et al., 1997]. Co-precipitation of GR with SWI/SNF components implies direct protein–protein interactions [Yoshinaga et al., 1992]. Thus, GR is able to recruit components of the chromatin remodeling machinery.

Recent evidence also suggests that members of the nuclear receptor superfamily switch, in a ligand-dependent manner, between binding of a multisubunit co-repressor complex containing factors with histone deacetyltransferase activity, and binding of a co-activator complex containing factors with histone acetyltransferase activity [Grunstein, 1997].

Steroid receptor co-activators (SRC)/nuclear receptor co-activators (NCoA) were initially identified biochemically as 160-kDa proteins (p160) that interact directly with nuclear receptors in an agonist and receptor AF-2 domain-dependent manner. To date there are three distinct but related p160 family members: SRC-1/NCoA-1, TIF2/GRIP1/NCoA-2, and p/CIP/ACTR/AIB1/RAC3/TRAM-1 [Torchia et al., 1998]. All have been shown to potentiate the transcriptional activity of several nuclear hormone receptors. The nuclear receptor interaction domain of cofactors p/CIP, SRC-1/NCoA-1, and TIF2/GRIP1 contain three highly conserved motifs that share a consensus amino acid sequence, LXXLL (where X is any amino acid) [Heery et al., 1997]. Similar motifs have been identified in virtually all cloned factors with the ability to interact with liganded receptors, including CBP, TIF1 and receptor intermediary protein 140 (RIP140) [Torchia et al., 1997]. Since a comparable motif is present in the AF-2 domain of nuclear receptors and mutational analysis has shown it to be functionally important, it is conceivable that the LXXLL motif provides the critical interactive surface to coordinate the entire nuclear receptor/co-activator complex.

Furthermore, evidence suggests that p/CAF is a component of the co-activator complex. Structurally, p/CAF contains a unique amino-terminal domain and a carboxy-terminal region that contains an histone acetyltransferase (HAT) domain. The intrinsic HAT activity of p/CAF can acetylate free histones H3 and H4 and nucleosomal H3 [Yang et al., 1996]. The C-terminal can potentially interact with components of the co-activator complex, including CBP and SRC-1/NCoA-1, as well as the nuclear receptors, progesterone receptor (PR) and retinoic acid receptor (RAR) [Korzus et al., 1998]. To date, HAT activity appears to be required for all regulated transcription factors. These activities allow co-activator complexes to relieve histone/chromatin-mediated transcriptional repression.

In the absence of hormone, some nuclear hormone receptors can bind DNA and act as transcriptional repressors. This repressor activity resides in the region of the LBD of RAR and thyroid receptor ($T_3R$) and is functionally separable from the AF-2 domain. These receptors bind to two related proteins, known as nuclear receptor co-repressor (NCoR) and silencing mediator for RXR and $T_3R$ (SMRT) that mediate transcriptional repression by $T_3R$ and RAR [Chen and Evans, 1995]. The core complex contains other stably associated polypeptides, including the histone deacetylases HDAC1 and HDAC2 [Hassig et al., 1997]. Other nuclear receptors that have been shown to interact with NCoR and SMRT are COUP-TF, REV-ErbA, PPAR$\gamma$, and, importantly, antagonist-bound estrogen receptor (ER) and PR [Torchia et al., 1997]. This suggests that nuclear receptors bind DNA and mediate repression by recruiting the NCoR/Sin3/RPD3 complex, resulting in histone deacetylation and repression of transcription. Ligand binding to hormone receptors results in the replacement of the NCoR/Sin3/RPD3 repressor complex, by a co-activator SRC-1/NCoA-1 complex with multiple potential HAT proteins which catalyzes histone acetylation [Torchia et al., 1997] (Fig. 2).

Furthermore, a direct interaction of the ER, the PR, and the COUP-TF with the general transcription factor TFIIB has been demonstrated [Beato and Sanchez-Pacheco, 1996]. Interactions, between steroid receptors and TFIIB could explain how receptors might recruit and enhance the formation of the preinitiation complex and in turn initiation of polymerase II transcription. Most likely direct interactions with the co-activators is required for the stabilization of the various complexes needed for proper binding of proteins to the promoter. This cooperative interaction (stabilization) between the steroid receptor/co-activator complex and the transcription machinery is probably not necessary in the repressive state when antagonist-receptor/co-repressor complexes are formed.

The nuclear receptors exhibit a high degree of temporal, tissue, and gene specificity. However, most of the co-activators or co-repressors,

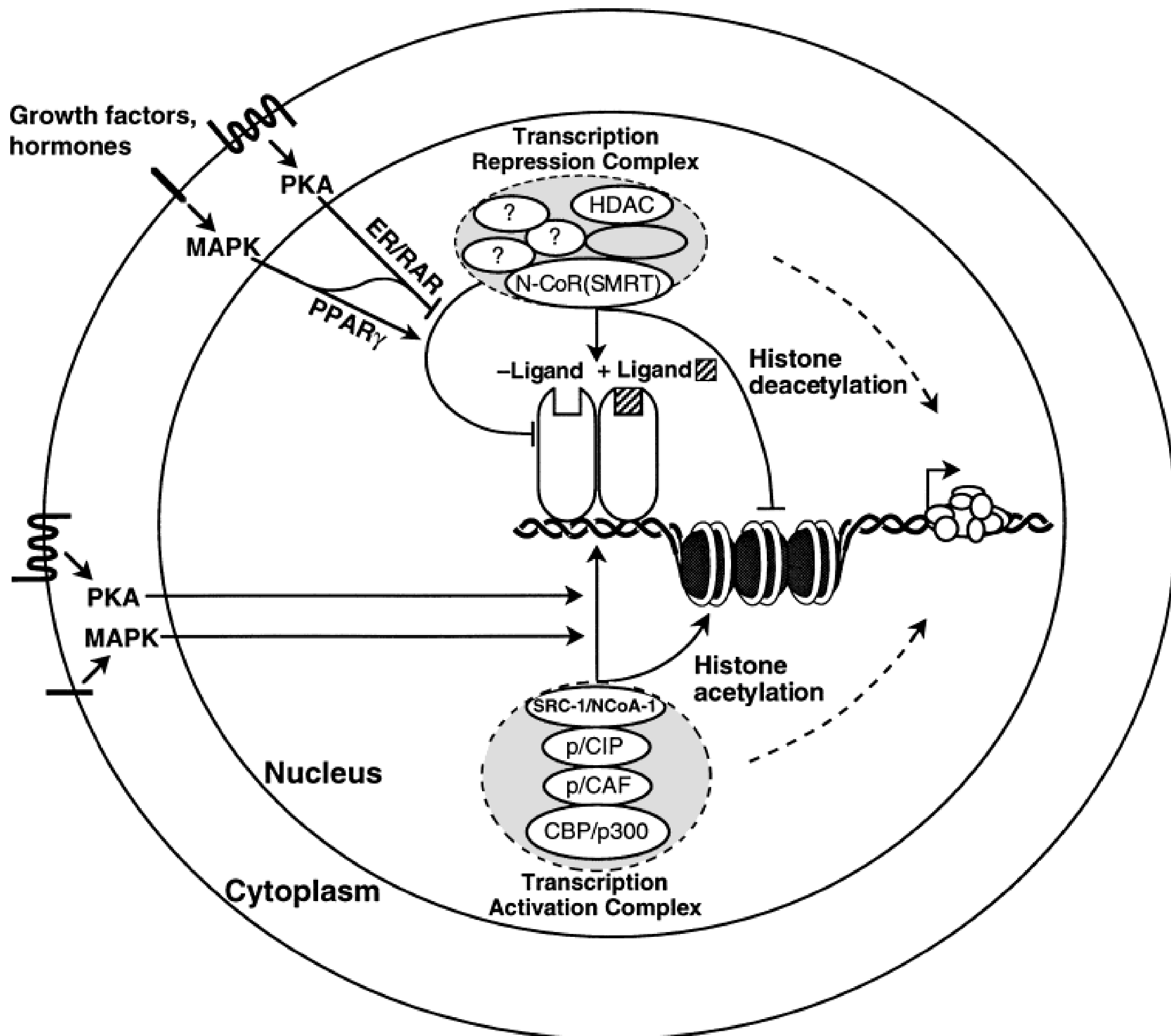


**Fig. 2.** Nuclear receptor function: switch from co-repressor to co-activation. In the absence of ligand, nuclear hormone receptors, in particular ER, RAR, and PPARγ, interact with a co-repressor complex, shown containing N-CoR(SMRT), the histone deacetylase HDAC and other proteins either not mentioned in this review or as yet undiscovered (*open ovals*). Ligand binding releases the co-repressor complex and allows the co-activator complex with its associated HAT activity to interact. This interaction results in histone acetylation and transcriptional activation. In addition, the inateractions between nuclear hormone receptors and the co-repressor or co-activator complexes may be regulated by a diverse array of nonsteroid-mediated transduction pathways, represented as the potential actions of protein kinase A (PKA) and MAP kinase pathways (MAPK) [Reprinted with permission from Torchia et al., 1998].

described above, have very little specificity in terms of where and when they are expressed and the nuclear receptors with which they interact. There may be still undiscovered co-activators whose expression is regulated spatially and temporally or interacts in a nuclear receptor specific manner. Interestingly, two such co-activators have been recently described. The co-activator, AIB1/SRC3 is overexpressed in many human breast cancers and increases the transcriptional activity of the estrogen receptor [Anzick et al., 1997]. Moreover, PPARγ co-activator (PGC)-1 was cloned from a brown fat cDNA library [Puigserver et al., 1998]. Expression of PGC-1 mRNA is dramatically increased in both brown fat and skeletal muscle in mice after being exposed to the cold. The addition of PGC-1 to combinations of either PPARγ/RXRα or TRβ/RXRα caused a dramatic ligand-dependent increase in uncoupling protein (UCP-1) promoter activity. Ectopic expression of PGC-1 in white adipose cells has been shown to acti-

vate the expression of UCP-1 and mitochondrial respiratory chain enzymes [Puigserver et al., 1998]. Differential interactions between the steroid receptors and the co-repressors may also prove important in understanding the molecular mechanism of some cancers. For example, acute promyelocytic leukemia (PML) involves the translocation and subsequent expression of fusion proteins between acute promyelocytic leukemia protein (PML) or PLM zinc-finger protein (PLZF) with the RARα [Hong et al., 1997]. Both fusion proteins interact with co-repressor complexes and the addition of retinoic acid causes the PML-RARα to dissociate from the co-repressor complex. By contrast, PLZF-RARα interacts constitutively with the co-repressor in the presence of retinoic acid [Hong et al., 1997]. These results could provide a potential mechanistic pathway and explain why PML-RARα APL patients achieve complete remission following retinoic acid treatment, whereas PLZF-RARα APL patients respond poorly to treatment. Clearly, further investigation is needed to isolate and characterize other tissue- and/or receptor-specific transactivation factors.

Most, if not, all the contacts between the components of the protein complexes (molecular machines) described above and the nuclear receptors involves predominantly the LXXLL motif of the transactivating factor binding to the AF-2 domain of the receptor. This raises the question of which factors are interacting with the AF-1 domain and what potential mediating effects on gene expression do these interactions cause. In one such case, PGC-1 uses a domain rich in proline residues to bind to the region that overlaps the hinge and DNA binding region of PPARγ [Puigserver et al., 1998]. This suggests that PGC-1 may act in concert with the other co-activators.

Moreover, the co-activators and the co-repressors represent a previously unrecognized target for nonligand-based signal transduction pathways. This may explain how certain nonligand-mediated signal transduction pathways can induce hormone-regulated target genes, even in the absence of ligand, or can further enhance the activation observed in the presence of hormone. In some cases, the post-translational modification occurs to the receptor itself [Hurd and Moudgil, 1998], but there are instances where no modification to the receptor can be detected. Suk-Hyun Hong et al., [1998] showed that activation of the tyrosine kinase signaling pathway by epidermal growth factor (EGF) receptor leads to a block of $T_3$R-mediated repression of gene transcription. These effects were reported to occur via a kinase-initiated disruption of the ability of $T_3$R to interact with SMRT co-repressor. Tyrosine kinase signaling was also able to disrupt the interactions with v-Erb A, with retinoic acid receptors, and with PLZF, a nonreceptor transcriptional repressor [Hong et al., 1998]. Another intriguing finding is that cAMP stimulation of cells converts the PR antagonist, RU486, and the ER antagonist, trans-OH tamoxifen, to agonists of their cognate receptors in a cell- and promoter-specific manner [Beck et al., 1993 and Fujimoto and Katzenellenbogen, 1994]. The exact mechanisms of these changing activities is not known. This implies important regulatory effects on transcriptional silencing may be mediated by a variety of signaling pathways that operate through the SMRT co-repressor complex.

## NONTRADITIONAL ACTIONS OF NUCLEAR RECEPTORS AND THEIR STEROID LIGANDS

### Cell Plasma Membrane Sites

It is generally held that steroids hormones such as progesterone ($P_4$) act at a genomic level by binding to its cognate receptor and modulating the expression of specific target genes. However, evidence demonstrates that $P_4$ or $P_4$ metabolites bind directly to the uterine oxytocin receptor (OTR), a member of the G-protein-coupled cell membrane receptor family. Progesterone inhibits oxytocin binding to OTR-containing membranes in vitro and suppresses oxytocin-induced inositol phosphate production [Grazzini et al., 1998]. The direct interaction between a steroid hormone and a G-protein-coupled receptor could define a new level of cross-talk between the steroid and peptide signaling pathways. Progesterone or its metabolites have also been shown to interact with the $GABA_A$ receptor, the NMDA receptor, the nicotinic acetylcholine receptor and the sperm cell membrane $P_4$ receptor [Puigserver et al., 1998 refs. within].

Working in another system, Sun et al. [1998] and Duan et al. [1998] demonstrated that there exists a functional synergy between the Sp-1 transcription factor and the ER. It was shown that a transcriptionally active ER/Sp-1 complex with GC-rich motifs is required for hormone inducibility of target genes such as RARα1,

c-*fos,* and cathepsin D genes all in MCF-7 human breast cancer cells. Importantly, c-*fos* protooncogene expression is induced by both $E_2$ and 4′-hydroxytamoxifen in MCF-7 cells, whereas ICI 164,384 exhibits ER antagonists activity. The differential expression is mediated via the GC-rich motif. Thus, genomic Sp-1 binding sites may play an important role in the $E_2$ responsiveness of some genes and also influence cell- and promoter/gene-specific differences in hormone-induced transactivation.

### Nuclear Matrix

Earlier observations by many groups have shown an association between various transcription factors and the nuclear matrix. These interactions appeared dynamic and to be cell type-specific, cell cycle dependent, developmentally, or hormonally controlled. In the case of the glucocorticoid receptor (GR), Tang et al. [1998] has identified a nuclear matrix targeting signal (NMTS) in the τ2 transactivation domain of rat GR. The transactivation and nuclear matrix-targeting activities of τ2 were separable, as transactivation mutants were identified that either inhibited or had no apparent effect on matrix targeting of τ2. Co-transfection experiments revealed a functional interaction between the NMTS of rat GR and the RNA-binding nuclear matrix protein hnRNP U. One can speculate that through its interaction with hnRNP U, the GR NMTS, may serve to target the receptor to the appropriate subnuclear compartment, where target genes are poised to respond to activated receptors and associated co-activators [Tang et al., 1998].

This laboratory has previously demonstrated that the steroid receptor binding factor (RBF) is a 10-kDa nuclear matrix-associated protein. When bound to avian genomic DNA, RBF generates saturable high-affinity binding sites for the avian PR [Schuchard et al., 1991a,b]. Recent studies have shown that RBF binds to a single-stranded 54-bp element in the 5′-flanking region of the progesterone-regulated avian c-*myc* gene. The RBF binding element contains a 5′-GC-rich domain and a 3′-AT-rich domain, flanked by nuclear matrix DNA attachment sites [Lauber et al., 1997]. The purified, reconstituted RBF appears to form direct protein–protein interactions with PRB in solution, inhibiting the ability of the PRB homodimer to bind a HRE and HRE/HMG2 complexes [Barrett et al., 1998]. These data support an overall structure of the nuclear matrix acceptor site for PR on the c-*myc* gene composed of RBF dimers bound to single-stranded DNA, which is flanked by nuclear matrix-like binding sites (Fig. 3). Other groups have reported rapid progestin stimulation of c-*myc* expression. However, the overexpression of transiently transfected RBF showed a decrease in reporter gene expression in progesterone-treated cells when driven by DNA sequences that contain the RBF element. The RBF/c-*myc* gene interaction and/or RBF/PR interaction might explain the paradoxical regulation of c-*myc* transcription by progesterone in different cellular systems, in particular, chick oviduct [Fink et al., 1988] versus human breast cancer cells [Moore et al., 1997].

## RECEPTORS AS TARGET SITES FOR OTHER RECEPTORS

Heterodimer formation among the members of the steroid receptor superfamily adds to the complexity and plasticity of this signaling pathway, particularly when multiple genes and isoforms exist for ER, GR, PR, RXR, TR, COUP-TF, and PPAR. As the expression of each isoform depends on cell type and the stage of growth and development, heterodimerization among all these receptors results in the formation of an extremely diverse group of receptors. Lee et al. [1998] have demonstrated that the ERα can form stable protein-protein interactions with hepatocyte nuclear factor 4, TR, RAR, ERβ, and RXR. Moreover, cotransfection of various combinations of these receptors with ERα results in differential patterns of transactivation regulation by ERα. This implies ER is a common interaction partner with these receptors, and these interactions should mediate novel signaling pathways in vivo.

The physiological implications of these non-traditional interactions among the steroid receptors has been accumulating. At activator protein1 (AP1) sites, 17β-estradiol activated transcription in the presence of ERα, whereas ERβ and 17β-estradiol inhibited transcription. Moreover, the antiestrogens tamoxifen, Raloxifene, and Imperial Chemical Industries (ICI) 164384 were potent transcriptional activators with ERβ at an AP1 site [Paech et al., 1997]. Thus the two ERs signal in different ways depending on ligand and response element. This suggest that ERα and ERβ may play different roles in gene regulation.

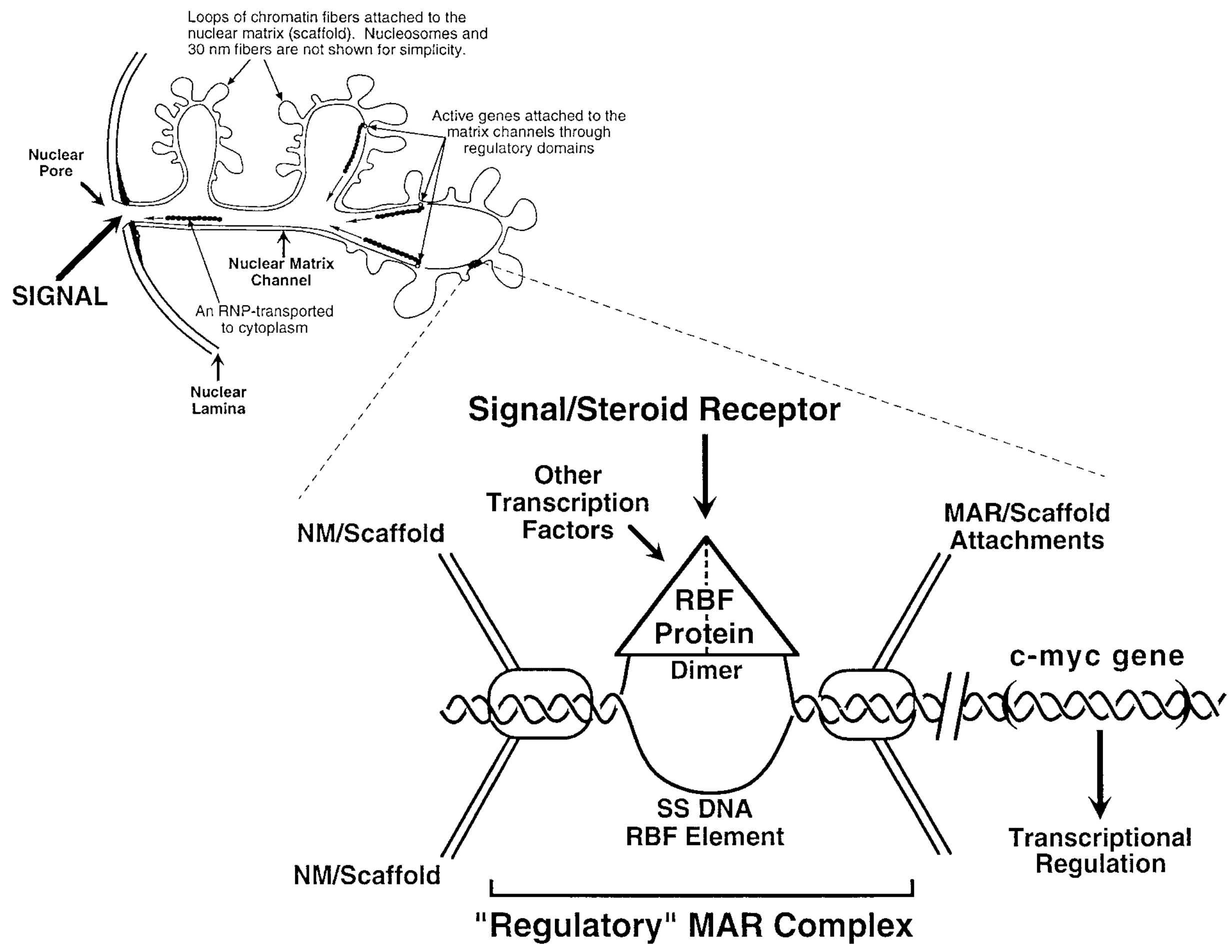


**Fig. 3.** Proposed model of RBF/DNA/steroid receptor interactions. **Left:** The solenoid is organized into loop domains, with the base of the loop attached to the nuclear matrix. The DNA regions attached to the nuclear matrix contain AT-rich domains and are referred to as matrix (scaffold)-associated regions (MARS or SARS or S/MARS). Razin and Gromova [1995] envisioned the nuclear matrix as a system of channels connecting the nuclear interior with the nuclear pores. Active DNA sequences, in terms of transcription and replication, are attached to these channels in such a way that the transport of important macromolecules from the cytoplasm to the nucleus is rapid and efficient. **Right:** Nuclear matrix DNA appears to attach to regions of DNA that flank the RBF element. This novel dual nuclear matrix attachment structure could play a role either in regulating the availability of the RBF/DNA complex for steroid receptor binding by forming twists, looping, or regions of ssDNA. Alternatively, the nuclear matrix could regulate steroid-induced gene transcription after steroid receptor binding by forming open or closed sites [Lauber et al., 1997 and Barrett et al., 1998].

## CONCLUSION AND PERSPECTIVES

In conclusion, our understanding of steroid receptor action has increased greatly over the last couple of years. However, the system has become more complex leading to still more important questions that need to be addressed. One question concerns the importance of the stoichiometries of the various co-activators and co-repressors and how modulating the relative amounts of the transactivators alters the transactivation ability of the nuclear receptors [Moras and Gronemeyer, 1998]. A second question concerns the potential role played by the AF-1 region of the receptors in modulating receptor actions and whether this region of the receptor molecule can be targeted for therapeutic drug design. A third question concerns the effects of posttranslational modification, for example, phosphorylation, of the co-activators and co-repressors on receptor transactivation ability and, again, whether this information can be used for therapeutic drug design. A fourth question concerns the allosteric effects of DNA on the nuclear receptors [Lefstin and Yamamoto, 1998]. The theory states DNA acts as an allosteric ligand whose binding alters the regulator's

affinity for other ligands, such as co-activators and co-repressors. In essence, specific DNA sequences would control which interactive surfaces are available to contact other target factors. A fifth question concerns the possible other nontraditional interactions of steroid hormone with other transduction pathways and steroid receptor interactions, for example, at the nuclear matrix and how these interactions alter cell function and gene expression. We look forward to the answers to these questions and to the new questions this research will generate.

## ACKNOWLEDGMENTS

We thank Jackie House for the preparation of the manuscript. We were unable to cite many interesting studies by many of our colleagues because of space constraints.

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