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Overview of Nomenclature of Nuclear Receptors

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***Abstract*——Nuclear receptor pharmacology has, to a certain extent, led the way, compared with other receptor systems, in the appreciation that ligands may exert very diverse pharmacology, based on their individual chemical structure and the allosteric changes induced in the receptor/accessory protein complex. This can lead to very selective pharmacological effects, which may not necessarily be predicted from the experience with other agonists/partial agonists/antagonists. If this is the case, then drug discovery may be back to drug-specific pharmacology (where each drug may have an original profile), rather than specific-drug pharmacology (where agents specific for a receptor have a distinct profile). As functional selectivity is indeed a crucial mechanism to be considered when going through the drug discovery development process, then initial screens using reconstituted systems may not show the appropriate pharmacology, simply because the required stoichiometry of corepressors and coactivators may not be present to select the best compounds; therefore, multiple effector systems are necessary to screen for differential activation, and, even then, screening with in vivo pathophysiological models may ultimately be required for the selection process—a massive but necessary task for pharmacologists. Thus, the characterization of nuclear receptors and their associated proteins and the ligands that interact with them will remain a challenge to pharmacologists.**

Introduction

Nuclear receptors (NRs[1]) are members of a large superfamily of evolutionarily related DNA-binding transcription factors that regulate programs involved in a broad spectrum of physiological phenomena (Laudet and Gronemeyer, 2002; Gronemeyer et al., 2004; Chambon, 2005; Evans, 2005).

Before the genes encoding these receptors were cloned, the first NR was identified biochemically in the 1960s (Jensen and Khan, 2004). Indeed, Elwood Jensen and his collaborators showed that estradiol was specifically retained in target cells of this hormone, leading to the discovery that its cellular activity is mediated by a specific high-affinity receptor (Jensen, 1962). Subsequently, and only 20 years ago, the human glucocorticoid receptor (GR, NR3C1) was one of the first NRs to be cloned by Ron Evans and his colleagues together with the estrogen receptor (ER) (that was the α subtype, NR3A1) cloned by the Pierre Chambon and Geoffrey Greene laboratories (Hollenberg et al., 1985; Green et al., 1986; Greene et al., 1986). Since then, NRs have become recognized as a superfamily of transcription factors, and the NR research field has undergone very rapid development and covers areas ranging from structural and functional analyses to the molecular mechanisms of transcription regulation.

From the phylogeny study of NRs, it has been established that NRs emerged in the earliest of metazoan evolution, long before the divergence of vertebrates and invertebrates (Escriva et al., 1997; Owen and Zelent, 2000). The sequencing of the human genome has led to

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[1] Abbreviations: NR, nuclear receptor; GR, glucuronide receptor; ER, estrogen receptor; SHP, small heterodimer partner; RXR, retinoid X receptor; RAR, retinoic acid receptor; TR, thyroid hormone receptor; AR, androgen receptor; MR, mineralocorticoid receptor; PR, progesterone receptor; PPAR, peroxisome proliferator-activated receptor; VDR, vitamin D receptor; ROR, retinoid-related orphan receptor; CAR, constitutive androstane receptor; PXR, pregnane X receptor; LXR, liver X receptor; COUP-TF, chicken ovalbumin upstream promoter transcription factor; H, helix/helices; L, loop(s); HNF-4, hepatocyte nuclear factor 4; NGFI-B, nerve growth factor-induced clone B; ERR, estrogen receptor-related; GCNF, germ cell nuclear factor; DBD, DNA-binding domain; LBD, ligand-binding domain; AF, activation function; HRE, hormone response element; 3D, three-dimensional; STAT, signal transducer and activator of transcription; LBP, ligand-binding pocket; LRH-1, liver receptor homolog 1; HAT, histone acetyltransferase; DR, direct repeat; CBP, cAMP response element-binding protein; SRC, steroid receptor coactivator 1; TIF, transcriptional intermediate factor; RAC, receptor-associated coactivator; TRAP, thyroid hormone receptor- associated protein; DRIP, vitamin D receptor-interacting protein; NCoR, nuclear receptor corepressor; SMRT, silencing mediator for retinoid and thyroid hormone receptors; HDAC, histone deacetylase; ChIP, chromatin immunoprecipitation; FRAP, fluorescence recovery after photobleaching; NF-κB, nuclear factor-κB; MAPK, mitogen-activated protein kinase; PK, protein kinase; DES, diethylstilbestrol; SNuRM, selective nuclear receptor modulator; SERM, selective estrogen receptor modulator.

the identification of 48 NRs. Each receptor has crucial and nonredundant roles, notably in the regulation of many biologically important processes in growth, development, and homeostasis. NRs modulate transcription through several distinct mechanisms, which include both activation and repression activities. These activities, making NR signaling remarkably complex, can be genomic or nongenomic and ligand-dependent or -independent, and can mediate gene repression, the release of gene repression, gene activation, or gene transrepression. NRs can also be the targets of other signaling pathways that modify the receptor post-translationally and affect its function.

Despite a highly evolutionary conserved structural organization, the function and the mode of action of NRs are very diverse. Indeed, except DAX-1 (NR0B1) and SHP (NR0B2), NRs bind sequence-specific promoter elements on target genes either as monomers or as homodimers or as heterodimers with the common retinoid X receptor (RXR). Moreover, among the 48 known NRs of the human genome, only 24 are liganded receptors. These classic receptors are ligand-dependent transcriptional factors that respond directly to a large variety of hormonal and metabolic substances. Ligands trigger changes in the conformational and dynamic behavior of the receptors that in turn regulate the recruitment of coregulators and chromatin-modifying machineries, a key component of NR signaling. Indeed, the ultimate action of liganded NRs on target genes, after site-specific DNA binding, is to enhance the recruitment and/or function of the general transcription machinery (Roeder, 1996). However, some NRs [for instance, the retinoic acid receptors (RARs) and the thyroid hormone receptors (TRs)] exhibit a dual functionality, being able to act as silencers of transcription in the absence of ligands, due to their ability to recruit corepressor complexes at the promoters of target genes, in addition to activating transcription in the presence of agonists. The receptors can also integrate diverse signaling pathways and regulate the activities of other major signaling cascades. In addition, some nongenomic actions have been described for steroid hormones outside of the nucleus that can be, at least partially, attributed to classic steroid receptors. Lastly, whereas some NRs are constitutively localized in the cell nucleus regardless of the presence of ligand, others [AR (NR3C4), MR (NR3C2), PR (NR3C3), or GR) are located in the cytoplasm in the absence of ligand. Binding of an agonist to these cytosolic receptors induces a nuclear translocation.

The other class of NRs are the so-called orphan receptors, for which regulatory ligands are still unknown or may not exist ("true orphans") or for which candidates have only recently been identified ("adopted orphans"). Controversy still exists regarding the evolutionary origin of the NR family as to whether the ancestral receptor was ligand-dependent or this feature evolved independently.

Because of the essential role played by NRs in virtually all aspects of mammalian development, metabolism, and physiology, dysfunction of signaling controlled by these receptors is associated with reproductive, proliferative, and metabolic diseases. The ability of some NRs for binding ligands makes them potential pharmaceutical targets. Accordingly, certain liganded NRs have one or more cognate natural or synthetic ligands that are used in therapy. Their successes as drug targets are highlighted by the common use of retinoic acid for RARα (NR1B1) (targeted in acute promyelocytic leukemia), the synthetic antagonist tamoxifen for ERα (NR3A1) (targeted in breast cancer), dexamethasone for GR (targeted in inflammatory diseases), or thiazolidinediones for peroxisome proliferator-activated receptor (PPAR) γ (targeted in type II diabetes).

Nomenclature

Sequence alignment and phylogenetic tree construction resulted in a classification of the human NR family into six evolutionary groups of unequal size (Nuclear Receptor Nomenclature Committee, 1999; Escriva et al., 2000; Thornton and DeSalle, 2000):

1. This large group contains the receptors TRs, RARs, VDR (NR1I1), and PPARs, as well as orphan receptors such as RORs, Rev-erbs, CAR (NR1I3), PXR (NR1I2), LXRs, and others.
2. This group includes RXRs, COUP-TF, and HNF-4.
3. This subfamily includes the steroid receptors with ERs, GRs, PRs, and ARs as well as the ERRs.
4. This small group contains the nerve growth factor-induced clone B group of orphan receptors [NGFI-B (NR4A1), NURR1 (NR4A2), and NOR1 (NR4A3)].
5. This another small group that includes the steroidogenic factor 1 (NR5A1) and the receptors related to the *Drosophila* FTZ-F1.
6. This subfamily contains only the GCNF1 receptor (NR6A1), which does not fit well into any other subfamilies.

A correlation exists between DNA-binding and dimerization abilities of each given NR and its phylogenetic position, which is not the case for ligand-binding ability.

The phylogenetic transparency of these receptors makes classification by sequence (but not necessarily by pharmacology, see below) relatively straightforward. Furthermore, trivial names have been proposed for some time. A proposition for a logical numbering system and receptor code, supporting the trivial names, was made in conjunction with the International Committee of Pharmacology Committee on Receptor Nomenclature and Classification (NC-IUPHAR) and has been accepted (Nuclear Receptor Nomenclature Committee, 1999; Gronemeyer et al., 2004). Thus, Table 1 lists the trivial names and the formal nomenclature. In each manuscript dealing with NRs, it is recommended that the

TABLE 1
Human nuclear receptors

Names	Nomenclature	Ligand
TRα	NR1A1	Thyroid hormones
TRβ	NR1A2	Thyroid hormones
RARα	NR1B1	Retinoic acid
RARβ	NR1B2	Retinoic acid
RARγ	NR1B3	Retinoic acid
PPARα	NR1C1	Fatty acids, leukotriene B_4, fibrates
PPARβ	NR1C2	Fatty acids
PPARγ	NR1C3	Fatty acids, prostaglandin J_2, thiazolidinediones
Rev-erbα	NR1D1	Orphan
Rev-erbβ	NR1D2	Orphan
RORα	NR1F1	Cholesterol, cholesteryl sulfate
RORβ	NR1F2	Retinoic acid
RORγ	NR1F3	Orphan
LXRα	NR1H3	Oxysterols, T0901317, GW3965
LXRβ	NR1H2	Oxysterols, T0901317, GW3965
FXRα	NR1H4	Bile acids, fexaramine
FXRβ^a	NR1H5	Lanosterol
VDR	NR1I1	Vitamin D, 1,25-dihydroxyvitamin D_3
PXR	NR1I2	Xenobiotics, 16α-cyanopregnenolone
CAR	NR1I3	Xenobiotics, phenobarbital
HNF4α	NR2A1	Orphan
HNF4γ	NR2A2	Orphan
RXRα	NR2B1	Retinoic acid
RXRβ	NR2B2	Retinoic acid
RXRγ	NR2B3	Retinoic acid
TR2	NR2C1	Orphan
TR4	NR2C2	Orphan
TLL	NR2E2	Orphan
PNR	NR2E3	Orphan
COUP-TFI	NR2F1	Orphan
COUP-TFII	NR2F2	Orphan
EAR2	NR2F6	Orphan
ERα	NR3A1	Estradiol-17β, tamoxifen, raloxifene
ERβ	NR3A2	Estradiol-17β, various synthetic compounds
ERR α	NR3B1	Orphan
ERRβ	NR3B2	DES, 4-OH tamoxifen
ERRγ	NR3B3	DES, 4-OH tamoxifen
GR	NR3C1	Cortisol, dexamethasone, RU486
MR	NR3C2	Aldosterone, spirolactone
PR	NR3C3	Progesterone, medroxyprogesterone acetate, RU486
AR	NR3C4	Testosterone, flutamide
NGFI-B	NR4A1	Orphan
NURR1	NR4A2	Orphan
NOR1	NR4A3	Orphan
SF1	NR5A1	Orphan
LRH-1	NR5A2	Orphan
GCNF	NR6A1	Orphan
DAX-1	NR0B1	Orphan
SHP	NR0B2	Orphan

[a] FXRβ is a pseudogene in human but is a functional lanosterol receptor in mouse (Robinson-Rechavi et al., 2001; Otte et al., 2003).

receptor(s) be identified by the official name(s) at least once in the Summary and the Introduction. No hyphen is necessary between NR and the subfamily, group, and gene numbers. Once the name has been established [e.g., "this article describes GCNF1 (NR6A1), a member of the nuclear receptor superfamily"], authors may use the trivial name for the remainder of the manuscript.

There is one outstanding problem, however, which has not been easy to resolve. PPARs are well characterized NRs. PPARα (NR1C1) was first described as a receptor that is activated by peroxisome proliferators, hence its name (Issemann and Green, 1990; Nuclear Receptor Nomenclature Committee, 1999; Gronemeyer et al., 2004). Two additional related subtypes, PPARβ (NR1C2) and PPARγ (NR1C3), were then found and characterized (Dreyer et al., 1992). The PPARβ subtype was called PPAR when it was first isolated from a *Xenopus* oocyte library (Dreyer et al., 1992). Because the mammalian PPARβ protein sequence was not highly homologous to the *Xenopus* PPAR protein sequences, it was named PPARδ when reported in the mouse as at the time it was thought that there may be four members of this NR family (Kliewer et al., 1994). PPARβ was also designated FAAR (fatty acid activated receptor) in the rat and NUC1 in the human being (Schmidt et al., 1992; Amri et al., 1995). However, sequencing of mammalian genomes clearly show that there are only three PPAR subtypes. It now seems clear that the mammalian PPARδ is the ortholog of the amphibian PPARβ. The formal nomenclature is NR1C2. However, two active camps have developed over the trivial name, with each using PPARβ or PPARδ for the same protein. The sub-

committee wishes, logically, to reclassify the trivial name as PPARβ, suppressing the use of PPARδ. However, PPARδ is cited more frequently, and corresponds better to the Human Genome Organisation gene name. We propose that a certain leniency in the short term be allowed, but as per the above discussion, we recommend that the receptor be identified by the official name (NR1C2) at least once in the Summary and the Introduction. Once the name has been established, either trivial name may be used for the remainder of the manuscript, but NC-IUPHAR prefers the more logical PPARβ.

Nomenclature: Terms and Symbols

The recommended usage of terms in the field of nuclear receptors is given in Table 2.

Structure/Function Analysis

All NR proteins exhibit a characteristic modular structure that consists of five to six domains of homology (designated A to F, from the N-terminal to the C-terminal end) on the basis of regions of conserved sequence and function (Fig. 1A) (Giguere et al., 1986; Krust et al., 1986). The DNA-binding domain (DBD, region C), absent in DAX-1 and SHP, and the ligand-binding domain (LBD; region E) are the most highly conserved domains. These two regions are the most important and can function independently as nicely demonstrated by the generation of a chimeric receptor in which the DBD of ER was swapped for that of GR. Strikingly, such a chimeric protein could bind estradiol but could not activate an estradiol-responsive gene, whereas it activated a glucocorticoid-responsive gene (Green et al., 1988). The variable N-terminal A/B domain and the D region are less conserved. The C-terminal F region, which is contiguous with the E domain, is not present in all receptors, and its function is poorly understood.

The A/B Region

The poorly defined N-terminal A/B region contains a transcriptional activation function, referred to as activation function 1 (AF-1), that can operate autonomously. In contrast to the other activation function (AF-2) located in the LBD of liganded NRs, AF-1 can act in a ligand-independent manner when placed outside of the receptor. However, in the context of its own full-length receptor, the activity of AF-1 is also controlled by ligand binding to the LBD. No crystal structure of an A/B domain has been elucidated so far. The length and sequence of the A/B region in the different NRs are highly variable, revealing a very weak evolutionary conservation. Interestingly, this domain has been shown to be the target of post-translational modifications as reported for the A/B domains of the RARs that include several consensus phosphorylation sites for proline-dependent kinases with specific attributed functions (Fig. 1F). In addition, this N-terminal region can interact with cofactors such as coactivators or other transcription factors. These features may be related to reported cell, DBD, and promoter specificity of the AF-1 activity. Lastly, N-terminal/C-terminal interaction has been shown, for example, for AR, ER, and PR (Ikonen et al., 1997). Note that the A/B domain is the major transactivation domain in the case of AR, but depends on androgen binding for activation (Simental et al., 1991).

TABLE 2
Terms for nuclear receptors
For nuclear receptors, the concept of agonist and antagonist is response- and gene-specific.

Terms	Definition/Description/Examples
Isoforms	Products of the same gene produced by alternative splicing, alternative promoter usage, alternative translational initiation; does not consider post-translational modifications; examples: RARα1 and RARα2
Subtypes	Products of related (paralogous) genes; subtype should be preferred to isotype; examples: RARα /RARβ/ RARγ
Coregulators	Macromolecules that associate with NRs to modulate their transcriptional activity; divisible into coregulators that promote positive activity (coactivators) and those that promote negative activity (corepressors)
Ligands for NRs	Compounds that bind reversibly to NRs into the C-terminal LBP
Unliganded receptor	Considered preferable compared with apo-receptor
Selective agonist and antagonist	Ligands with an affinity difference (preferably greater than 100-fold) between their primary target and other receptors
Agonists	Ligands that induce an active conformation of the receptor
Antagonists	Ligands that produce a conformation and an action of the receptor distinct from that produced by an agonist
SNuRM	Selective ligand with partial function-, cell-, and/or promoter-specific action
Partial agonists	Agonists that in a given tissue, under specific conditions, cannot elicit as optimal an effect (even when applied at high concentration, so that all the receptors should be occupied) as can another agonist acting through the same receptors in the same tissue
Inverse agonists	Ligands that can promote corepressor recruitment
Potency	An expression of the activity of a drug, in terms of the concentration or amount needed to produce a defined effect—an imprecise term that should always be further defined (e.g., EC_{50}, IC_{50}, etc.); drug potency depends on both receptor (affinity, efficacy) and tissue (receptor numbers, drug accessibility) parameters; term is sometimes incorrectly used to refer to the maximum effect attainable
Transactivation	Activation of transcription by the binding of a transcription factor (and coregulators?) to a DNA regulatory sequence

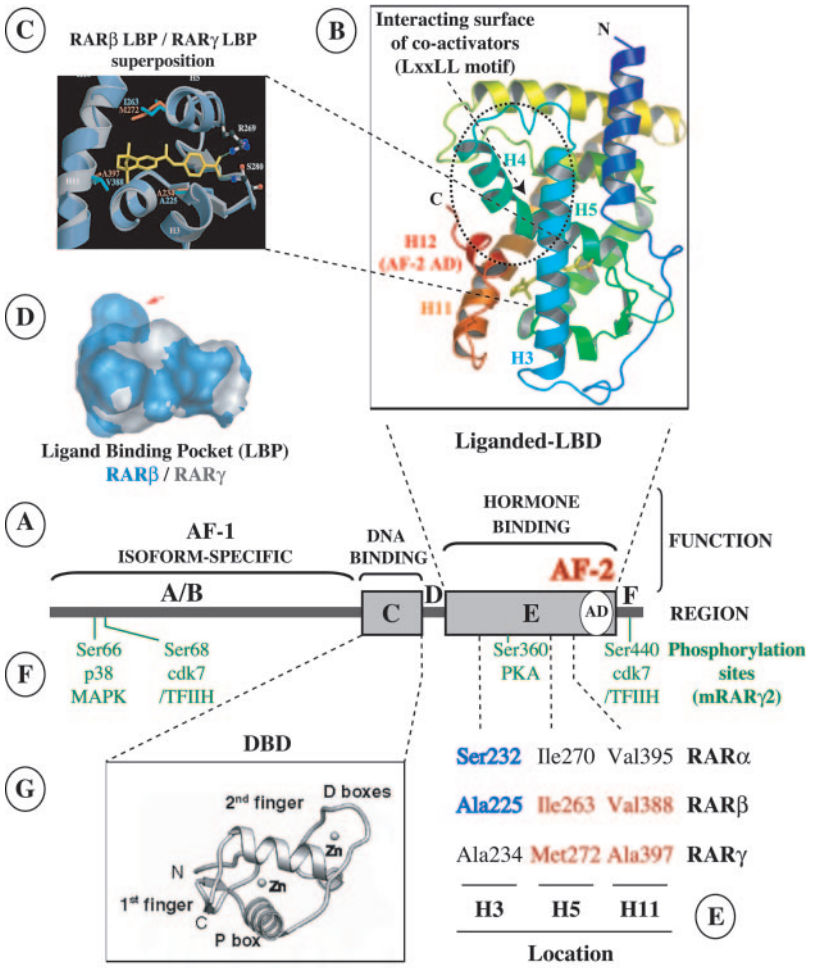

FIG. 1. Structural and functional organization of nuclear receptor superfamily. A, nuclear receptors consist of six domains (A–F) based on regions of conserved sequence and function. The evolutionarily conserved regions C and E are indicated as boxes, and a black bar represents the divergent A/B, D, and F regions. Domain functions are given above the scheme. B, schematic drawing of the agonist-bound NR LBDs. The α helices (H1–H12) are depicted as ribbons, and the β-turn as broad arrows. The activation helix, H12, which harbors the residues of the core AF-2, is shown in red. The surface that interacts with coactivators (the LxxLL motif) is highlighted by the dotted oval line. Image courtesy of Dr. William Bourguet, Institut National de la Santé et de la Recherche Médicale, Centre de Biochimie Structurale, Montpellier, France. C, superposition of [(*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)propen-1-yl]benzoic acid] (TTNPB)-RARβ (blue) and 9-*cis*-retinoic acid-RARγ (gray) LBDs. The subtype-specific residues are shown in cyan (RARβ) and orange (RARγ), and TTNPB is in yellow. The carboxylate anchoring residues are illustrated as ball-and-sticks. H bonds are represented as dashed lines. Image courtesy of Dr. Sabrina Kammerer, Swiss Federal Institute of Technology, Zurich, Switzerland. D, superimposition of RARβ (blue) and RARγ (gray) LBPs. Crystal structure of the RARβ LBD-TTNPB complex reveals an additional cavity in the RARβ LBP. The arrow points to the additional cavity in RARβ. Image courtesy of Dr. Sabrina Kammerer. E, the three divergent residues in the LBPs of RARα, RARβ, and RARγ are located in helices 3, 5, and 11. The residues that differ between RARα and RARβ LBPs are displayed in blue; those differing between RARβ and RARγ are shown in red. F, schematic representation of the major phosphorylation sites (in green) of mouse RARγ2. The 3D structure of ERα DBD was obtained from X-ray crystal structure analyses. The various structural elements (Zn^{2+} fingers and D and P boxes) are indicated. Image courtesy of Dr. William Bourguet.

The DNA-Binding Domain

The central C region of the NRs is the DBD that is the most conserved domain (Fig. 1A). In vitro investigations demonstrated that, through this domain, NRs bind to specific DNA sequences, called hormone response elements (HREs) (except for DAX1 and SHP which do not harbor a DBD) (Kumar et al., 1986). Nuclear magnetic resonance and crystallographic studies were performed for different NR DBDs in their DNA uncomplexed and complexed forms, with the GR and ER homodimers on their cognate DNA sequence being the first 3D crystal structure reported (Fig. 1G) (Luisi et al., 1991; Schwabe et al., 1993). These approaches revealed that the DBD consists of a highly conserved 66-residue core made up of two typical cysteine-rich zinc finger motifs, two α helices, and a COOH extension. It includes several sequence elements, referred to as P, D, T, and A boxes, that have been shown to define or contribute to the response element specificity, to a dimerization interface within the DBDs, and to contacts with the DNA backbone and residues flanking the DNA core recognition sequence (Umesono and Evans, 1989). The P box is the highly conserved part in the first zinc finger between the last two cysteines and determines the sequence specificity of the receptor-DNA binding response element (Zilliacus et al., 1994; Laudet, 1997). Strikingly, a single amino acid change within the P box can interconvert ER and GR response element selectivity. Another conserved part in

the second zinc finger is the D box, which dictates the half-site spacing. Depending on the type of receptor, the C-terminal extension plays a role in sequence recognition and/or dimerization.

The DBD is also the target of post-translational modifications. Furthermore, it is involved in nuclear localization and functions in interactions with transcription factors and coactivators. For instance, the AR DBD interacts with protein inhibitor of activated STAT-1, which increases AR-mediated gene activation (Tan et al., 2002).

The D Region

The D region, which is a poorly conserved domain, is considered to serve as a hinge between the DBD and the LBD, allowing rotation of the DBD (Fig. 1A). Therefore, it might permit the DBDs and the LBDs to adopt different conformations without creating steric hindrance troubles. This domain also harbors a nuclear localization signal or at least some elements of a functional nuclear localization signal.

The Ligand-Binding Domain

Numerous in vitro studies have shown that the LBD, which is less conserved than the DBD, is functionally complex as it mediates ligand binding and dimerization and contains a ligand-dependent transactivation function. The LBD contains four structurally distinct but functionally linked surfaces (Fig. 1B): 1) a dimerization surface, which mediates interaction with partner LBDs, 2) the ligand-binding pocket (LBP), which interacts with diverse lipophilic small molecules in the case of liganded NRs, 3) a coregulator binding surface, which binds to regulatory protein complexes that modulate positively or negatively transcriptional activity, and 4) an activation function helix, termed AF-2, which mediates ligand-dependent transactivation. Within the AF-2, the integrity of a conserved amphipathic α-helix called AF-2 activation domain has been shown to be required for ligand-dependent transactivation and coactivator recruitment. Moreover, some NRs can also interact with transcriptional corepressors through their LBD. In addition, other members of the NR superfamily interact with heat-shock proteins via their LBD (GR, MR, PR, AR, and ER) (for a review see Pratt and Toft, 1997).

Structure of the Ligand-Binding Domain

The LBDs of NRs are complex allosteric signaling domains that are able to integrate multiple molecular interactions at four more-or-less overlapping structurally distinct sites to modulate transcriptional activation (Bourguet et al., 2000a). Currently, the LBD crystal structures of all classic liganded receptors and adopted orphan receptors have been determined. These structures were solved with LBDs alone or in complex with agonists or antagonists, some with peptides corresponding to fragments of transcriptional coactivators or corepressors, and in the form of monomers, dimers, or tetramers. In contrast, the crystal structures of most orphan receptors remain unknown.

The first resolution of a NR LBD crystal structure, the unliganded RXRα, revealed that this domain is highly structured (Bourguet et al., 1995). This crystal structure, together with the elucidation of the 3D structures of multiple other NR LBDs, showed a common fold comprising 12 α helices (H) and a short β-turn (s1-s2), arranged in three layers to form an antiparallel "α-helical sandwich." Helices 1 through 3 constitute one face of the LBD. H4, H5, s1-s2, H8, and H9 correspond to the central layer of the domain and H6, H7, and H10 form the second face. The superposition of all available LBD structures reveals a clear overall similarity, particularly in the top half of the LBD, that includes H1, H4, H5, and H7 through H10 and corresponds to a structurally rather invariable region. The lower part of the LBD harbors a variable region, which contains the LBP.

Dimer Interface

NRs can form monomers, homodimers, or heterodimers with RXR. To date, the crystal structures of monomeric, homodimeric, and heterodimeric NR LBDs have been described, allowing comparison of the homo- and heterodimerization interfaces of several NR LBDs. The overall heterodimeric arrangement closely resembles that of a homodimer. A comparison of the heterodimer formed by the RARα LBD and the RXRα LBD with the homodimer formed by ERα LBD reveals that the structural elements generating the dimerization interface are identical. The interfaces comprise residues from H7, H9, H10, and H11, as well as loops (L) 8–9 and L9–10, with H9 and H10 contributing to >75% of the total surface and constituting the core of the dimer interfaces (Bourguet et al., 2000b; Gampe et al., 2000). However, in contrast to the nearly perfect symmetric organization of homodimer interfaces, the heterodimer interfaces are slightly asymmetric. In ERα, H8, H9, and H10 and L8–9 are longer and make additional contacts. As a consequence, the buried surfaces are larger for the ERα homodimer (around 1700 $Å^2$) than the buried surfaces for the RXRα-RARα heterodimer (915 $Å^2$), suggesting a higher dimerization affinity for ERα than for RXR dimers. It has been proposed that in NRs that form heterodimers with RXR, ligand binding also affects the stability and propagation of signals across the heterodimerization interface, indicating that the ligand-binding pocket and dimerization interface are in some way energetically linked (Cheskis and Freedman, 1996; Thompson et al., 1998; Shulman et al., 2004).

The 3D structure of the GR LBD dimer suggests an alternative mode of dimerization that involves residues from the β-turn of strands 3 and 4 and the extended strand between H1 and H3, as well as the last residue of H5 (Bledsoe et al., 2002). Compared with the dimerization surfaces observed in the other NRs, formation of the

GR homodimer buries only 623 Å^2 of solvent-accessible surface, probably reflecting its weaker dimerization affinity.

The Ligand-Binding Pocket

The LBP is an important structural feature of NRs, at least for the liganded-receptors, since the first step of receptor activation is initiated by ligand-binding. It is generally located behind helix 3 and in the front of helices 7 and 10 and is lined with mostly hydrophobic amino acids. Few polar residues at the deep end of the pocket near the β-turn act as anchoring points for the cognate ligand or play an essential role in the correct positioning and enforce the selectivity of the pocket. The specificity of ligand-binding is also determined by the shape of the LBP, which can vary greatly from receptor subtype to subtype (Germain et al., 2004). Despite the conserved fold of LBDs, the LBP also varies greatly in size, from Nurr1, which lacks a cavity, to SF-1, which has a pocket of ~1600 Å^3 (Wang et al., 2003; Li et al., 2005). Strikingly, the space that is occupied by ligands in classic liganded and adopted receptors is entirely filled by hydrophobic amino acid side chains in "true" orphans such as Nurr1, indicating that not all NRs work as ligand-binding receptors (Wang et al., 2003). Surprisingly, the LBD structure of another true orphan receptor, LRH-1, showed the presence of a large LBP of ~800 Å^3 that is completely enclosed (Sablin et al., 2003).

The AF-2 Function

The ability of NR LBDs to activate transcription is controlled by the C-terminal helix 12, termed AF-2. The crystal structures of the unliganded and ligand-bound LBDs of several NRs suggested a common mechanism by which AF-2 becomes transcriptionally competent (for reviews, see Bourguet et al., 2000a; Li et al., 2003). For instance, in the unliganded form, H12 of RXR extends downward from the LBD (Bourguet et al., 1995). Upon ligand binding, a series of intramolecular interactions cause the repositioning of H11 in the continuity of H10, and the concomitant swinging of H12. These structures highlighted the crucial conformational flexibility of the AF-2 helix 12. Consequently, the induction of the AF-2 upon ligand-binding involves the proper repositioning of structural elements (H3, H4, L3–4, and H12) such that a defined NR interaction surface for transcriptional coactivators is generated. The importance of the AF-2 helix in regulating coactivator and corepressor binding is detailed below.

Transcriptional Regulation by the Nuclear Receptors

NRs are highly regulated DNA-binding transcription factors that control transcription via several distinct mechanisms, which include both activation and repression activities. After site-specific DNA binding, their final transcriptional activity depends on the set of associated proteins, the so-called coactivators and corepressors, interacting with them. These coregulators are not exclusive to NRs and are used in a similar manner by numerous other DNA-binding transcription factors (Cosma, 2002; Hermanson et al., 2002; Kraus and Wong, 2002; Privalsky, 2004). NRs have been used as powerful tools for understanding the specific, as well as the more general, mechanisms of transcriptional regulation, and recent studies involving NRs have provided insights into the molecular mechanisms that are required to switch between repression and activation, but also the combinatorial roles of the multiple cofactors that are required for mediating transcriptional regulation.

The organization of DNA into chromatin in eukaryotic genomes induces regulatory constraints that play central roles in many cellular processes (Khorasanizadeh, 2004). Indeed, chromatin structure exerts a crucial influence on transcription by limiting the access of promoter sequences to the transcription machinery and organizing genomic information for the coordinated regulation of genome expression (Perkins et al., 2004). For instance, it is well known that transcriptionally active euchromatin regions of the eukaryotic genomes exhibit hyperacetylation of histones, whereas transcriptionally inactive heterochromatin regions are marked by hypoacetylation (Vaquero et al., 2003). Many of the changes in chromatin structure by transcription factors involve complex patterns of histone modifications by enzymes such as histone acetyltransferases (HATs), histone methyltransferases, and kinases. All of these chromatin modifications have led to the hypothesis of a histone code, which suggests that specific combinations of covalent histone modifications determine specific transcriptional responses and, consequently, cellular functions (Strahl and Allis, 2000; Turner, 2002). Hence, histones are crucial targets for the enzymatic activities of cofactors that are recruited by NRs.

NR signaling is remarkably complex because many receptors respond to cellular signals through ligand-dependent or -independent mechanisms and because many accessory coregulators dictate cell-specific transcriptional responses to a given receptor. Moreover, NR activities can be nongenomic and can mediate gene transrepression. Therefore, NRs also provide an interesting model for understanding how several different signaling pathways can be integrated to achieve specific profiles of gene expression.

DNA Recognition

An essential step of NR action is the interaction of these receptors with the specific DNA sequence HREs. Indeed, HREs position the receptors and the transcriptional complexes recruited by them close to the target genes. HREs are bipartite elements that are composed of two hexameric core half-site motifs. These consensus nucleotide sequences form direct, indirect, or inverted

repeats, which consist of two half-sites separated by a short spacer (Mangelsdorf and Evans, 1995; Chambon, 1996; Laudet and Gronemeyer, 2002). Hence, the identity of the response elements can be determined by 1) the nucleotide sequence of the two core motif half-sites, 2) the number of base pairs separating them, and 3) the relative orientation of the motifs.

The NR superfamily can be divided into subgroups on the basis of their pattern of dimerization. One group consists of the steroid receptors, all of which seem to function as homodimers, that bind to a degenerate set of response elements containing inverted repeats of a hexameric half-site separated by 3 base pairs of spacer (IR3) (Beato et al., 1995). Except ER, the steroid receptors (GR, MR, AR, and PR) recognize the consensus sequence 5′-AGAACA-3′. ER binds similar symmetric sites but with consensus 5′-AGGTCA-3′ half-sites. The crystal structure of the GR and ER DBDs bound to IR3 elements revealed a "head-to-head" protein dimer bound to DNA (Luisi et al., 1991; Schwabe et al., 1993).

Nearly all known nonsteroid receptors recognize one or two copies of the consensus DNA sequence 5′-AGGTCA-3′. Among these receptors, a major group consists of receptors that form heterodimers with RXR. The various RXR heterodimers can bind to direct repeats (DRs) with one to five base pairs of spacing, referred to as DR1 to DR5. The one to five rule specifies the use of DRs with variable spacings by RXR and its many partners. As seen in the crystal structures of NR DBDs bound to DR elements, the receptors bind as "head-to-tail" heterodimers (Rastinejad et al., 1995, 2000; Zhao et al., 2000; Shaffer and Gewirth, 2002).

Some NRs can also bind DNA efficiently as monomers such as NGFI-B, Rev-erb, ROR, and SF-1 (Wilson et al., 1993; Giguere et al., 1995; Harding and Lazar, 1995; Charles et al., 1999). Note that, for instance, NGFI-B also forms a heterodimer with RXR, which can bind to a DR5.

So far, it has proved difficult to visualize the full-length NRs in complex with DNA. However, except for VDR, the isolated DBDs and associated C-terminal extension domains are necessary and sufficient to generate the same pattern of DNA response element selectivity, partner selection, and dimerization as the full-length receptors (Mader et al., 1993; Perlmann et al., 1993; Towers et al., 1993; Zechel et al., 1994a,b; Shaffer and Gewirth, 2002).

Transcriptional Activation

In the case of liganded NRs, ligand-binding is the first and crucial molecular event that switches the function of these transcription factors from an inactive to active state by inducing a conformational change in the LBD of the receptor (Bourguet et al., 2000a). This specific conformation allows the second step of NR activation that corresponds to the recruitment of coregulatory complexes, which contain chromatin-modifying enzymes required for transcription (Shang et al., 2000). The ultimate action of liganded NRs on target genes is to enhance the recruitment and/or function of the general transcription machinery (RNA polymerase II and general transcription factors) (Roeder, 1996).

The transcriptional coactivators are very diverse and have expanded to >100 in number. The p160 family of proteins, cAMP response element-binding protein (CBP), and p300 are considered to be among the first recruited by activated NRs (Chen et al., 2000; Vo and Goodman, 2001; McKenna and O'Malley, 2002). The p160 family includes SRC-1, TIF2 (also known as SRC-2 and GRIP1), and RAC3 (also known as SRC-3, ACTR, pCIP, and TRAM-1) (Chen, 2000). Biochemical and structural data clearly showed that p160 proteins can physically interact with agonist-bound NR LBDs through a highly conserved α-helical LxxLL motif (NR box), in which L corresponds to leucine and x to any amino acid. This NR box is necessary and sufficient for ligand-dependent direct interaction with the cognate surface in the NR LBD. Both CBP and p300 are reported to act as HATs (Vo and Goodman, 2001). They are able to acetylate lysine residues in the N-terminal tails of different histones, thereby weakening the interaction of the histone tails with the nucleosome DNA, which is believed to prepare target promoters for transactivation by decondensation of the corresponding chromatin. Coactivator complexes also include factors that are structurally and functionally distinguishable from the p160 family and that contain ATP-dependent remodeling or histone arginine methyltransferase activities (Fryer and Archer, 1998; Dilworth et al., 2000; DiRenzo et al., 2000; Koh et al., 2001; Wang et al., 2001b; Xu et al., 2004). The sequential model of NR-mediated transcriptional initiation suggests that the p160 proteins dissociate, subsequent to their acetylation, which decreases their ability to interact with the receptors, or their degradation by the proteasome (Chen et al., 1999; Yan et al., 2003). This initial chromatin-modifying step carried out by p160 coactivators has to be followed by the actual recruitment of the RNA polymerase II holoenzyme. Activated NRs can recruit the transcription machinery through their association with members of the mammalian mediator [thyroid hormone receptor-associated protein (TRAP)-vitamin D receptor-interacting protein (DRIP) complex], which directly contacts components of the basal transcription machinery. Note that the most detailed information regarding mediator function has come from studies of NR interactions (Malik and Roeder, 2000). Although this complex seems to be required at all genes, specific subunits are dedicated to regulation of distinct expression programs via interactions with relevant gene-specific transcriptional activators. The subunit of the TRAP/DRIP complex that is responsible for interaction with the LBD of activated receptors was identified as TRAP220/DRIP205 and harbors a functional LxxLL NR box motif (Yuan et al., 1998; Rachez et al., 1999;

Yang and Freedman, 1999). New coregulators are continually being discovered, and these include factors that were not expected to serve such functions, e.g., the RNA transcript for the steroid receptor-RNA activator-1 coactivator, the NAD/NADH sensor C-terminal binding protein of E1A, and several actin-binding proteins (Lanz et al., 1999; Vo et al., 2001; Kumar et al., 2002; Ting et al., 2002; Loy et al., 2003; Nishimura et al., 2003; Yoon et al., 2003; Huang et al., 2004; Kumar et al., 2004; Lee et al., 2004). An exhaustive list of known coregulators can be found in several reviews (Cosma, 2002; Hermanson et al., 2002; Kraus and Wong, 2002; Privalsky, 2004).

Transcriptional Repression

Early on, it was shown that, in addition to activation of gene expression upon ligand-binding, some NRs that bind constitutively to target promoters can also exhibit a repression function (Baniahmad et al., 1995). This silencing function has been well established for unliganded retinoic acid and thyroid hormone receptors. Repression is mediated by interaction with transcriptional corepressors such as nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT) that were originally identified as components of a complex involved in repression associated with unliganded RAR and TR (Chen and Evans, 1995; Horlein et al., 1995; Ordentlich et al., 1999; Park et al., 1999). The C-terminal part of both NCoR and SMRT contains a region that specifically recognizes and binds to a hydrophobic groove in the surface of the LBD of unliganded RAR and TR, as well as LBD of steroid hormone receptors bound to certain antagonists. Although NCoR and SMRT do not harbor intrinsic enzymatic activity, each resides in, or recruits, high-molecular-weight transcriptional complexes that contain specific histone deacetylases (HDACs). Such complexes display the opposite activity of coactivator complexes that acetylate histones. Indeed, HDACs have a well-characterized role in transcriptional repression by deacetylating lysine residues in the N-terminal tails of histone proteins and generating a condensed chromatin structure over the target promoter. The loss of acetylation leads to the increased positive charge of lysine that favors a closed nucleosomal structure and reduces the affinity of coactivators containing bromodomains. NCoR and SMRT can actively contribute to the repression process since it has been shown that the enzymatic activity of HDAC3 requires interaction with a region of both NCoR and SMRT, referred to as the deacetylase-activating domain, located in the amino terminus of these two corepressors (Hartman et al., 2005).

In general, unliganded NRs preferentially interact with corepressors to mediate repression, whereas liganded receptors are transcriptional activators owing to their ability to recruit coactivator proteins. Nevertheless, exceptions have been identified. Some corepressors, exemplified by ligand-dependent nuclear-receptor corepressor, receptor-interacting protein-140, and receptor of estrogen-receptor activity, can bind to NRs in a ligand-dependent manner and compete with coactivators by displacing them (Delage-Mourroux et al., 2000; White et al., 2004).

Other members of the NR superfamily also can mediate transcriptional repression via an alternative mechanism. With DAX-1, SHP belongs to a heterogeneous group of NR-related proteins that are substantially distinct from conventional NRs in both structure and function. Members of this family have no DBD and act as a repressor. Indeed, SHP acts as an inhibitory partner for a variety of NRs and was shown to bind to the NR AF-2 activation domain via LxxLL-related motifs, leading to the two-step model of NR inhibition by SHP, involving coactivator competition and active repression (Bavner et al., 2005).

Molecular Basis of Corepressor/Coactivator Exchange

In living cells, the ligand-induced exchange of corepressor and coactivator occurs in the context of chromatin (Glass and Rosenfeld, 2000). The structural basis that regulates the alternative interactions of the NR with either class of coregulators has been revealed by crystallographic studies (Nagy and Schwabe, 2004). Several classic NR LBDs were cocrystallized together with their cognate agonist and a short peptide from the nuclear receptor interaction domain of coactivators that contained the so-called LxxLL motif (Heery et al., 1997). In all cases, the coactivator peptide is bound to a hydrophobic groove generated by the C-terminal part of H3, L3–4 and H4. The peptide is held in place through the interactions of its two leucine residues with the hydrophobic groove constituents but also by hydrogen bonds that involve two conserved amino acids of NR LBDs. These residues are a lysine at the C terminus of H3 and a glutamate in the AF-2 helix 12, which is in the ligand-induced proper position. Both are hydrogen-bonded to a main-chain peptide bond of the LxxLL motif and together form a "charge clamp" that, in addition to the stabilization of the peptide-receptor interaction defines the precise length of the helical motif that can be docked to the cleft.

In the absence of hormone, NRs such as RARα and TR may assume an alternative conformation, notably regarding the position of the helix 12 that stably interacts with the corepressor NCoR and SMRT. In evaluation of corepressor binding to mutants in the hydrophobic coactivator binding site of TRα, it has been demonstrated that mutations that impaired activation and coactivator binding also decreased repression and corepressor recruitment, indicating that corepressors bind to a NR LBD surface topologically related to that involved in coactivator interaction (Hu and Lazar, 1999). The C terminus part of the corepressor contains two separate NR-interacting domains, termed ID1 and ID2. Within each ID, an LxxLL-like corepressor motif (also called

CoRNR box or LxxxIxxxI/L motif) is responsible for interactions with NRs. Both IDs are similar but not identical to the coactivator LxxLL motif and can be viewed as an N-terminally extended helix when compared with the shorter coactivator LxxLL helix. Therefore, this observation suggests that the ligand-dependent exchange between corepressors and coactivators originates from the difference in length of the interacting motifs that can be accommodated in the hydrophobic groove in the two conformations (Perissi et al., 1999). Accordingly, the crystal structure of a ternary complex containing the PPARα LBD bound to the antagonist GW6471 and a SMRT ID2 motif demonstrates that the corepressor peptide adopts a three-turn helix that binds into the hydrophobic groove, which is also involved in the coactivator binding (Xu et al., 2002). Therefore, in contrast to the unliganded NR, the length of the helix that can be accommodated by the H12-containing groove in presence of an agonist is strictly defined by the presence of the charge clamp that specifically recognizes helices of the coactivator NR box type (Nolte et al., 1998). Consequently, the ligand-induced conformational change causes dissociation of the corepressors, allowing the receptor to interact with coactivators (for a review, see Nagy and Schwabe, 2004).

Kinetics and Nuclear Receptor Turnover

So far, the conventional view of NR action was that NRs remain stably bound to their HREs and that the transcription initiation is static. However, in the past few years, kinetic descriptions of transcriptional activation have been provided. Chromatin immunoprecipitation (ChIP) assays and fluorescence recovery after photobleaching (FRAP) have revealed the dynamic and the cyclic nature of gene expression controlled by NRs. ChIP analyses of promoter occupancy by different NRs have shown a cyclic turnover of NRs on regulated promoters (Shang et al., 2000; Kang et al., 2002; Reid et al., 2003). The most detailed ChIP-based analysis of the dynamic mechanisms involved in transcriptional initiation has been obtained for ERα-mediated gene expression on different promoters (Shang et al., 2000; Metivier et al., 2003; Reid et al., 2003; Liu and Bagchi, 2004; Park et al., 2005). For instance, the duration of each cycle is approximately 20 min in the case of ERα binding to the pS2 promoter in presence of estrogen (Metivier et al., 2003). Furthermore, this study has revealed the ordered and cyclic recruitment of various components of transcription complexes, illustrating the dynamic nature of transcriptional activation. The cycle of NR recruitment and release on target promoters might be crucial and seems to correlate with proteasome-dependent degradation activity and chromatin remodeling events (Freeman and Yamamoto, 2002; Reid et al., 2003; Nagaich et al., 2004). Accordingly, NRs and most of their coregulators can be ubiquitinylated and regulated by protein degradation, and the degradation of transcriptional activators is often required for gene activation (Alarid et al., 1999; Nawaz et al., 1999; Zhu et al., 1999; Dace et al., 2000; Floyd and Stephens, 2002; Yan et al., 2003). Furthermore, the site of ubiquitinylation and the transcriptional domain overlap in many transcription factors (Molinari et al., 1999; Lonard et al., 2000; Salghetti et al., 2000; Gianni et al., 2002; Kang et al., 2002; Lin et al., 2002; Reid et al., 2003). On the other hand, the turnover of GR on synthetic promoters has been studied by FRAP. Whereas ChIP has a time resolution of several minutes, FRAP resolves events in the second range. This photobleaching technique allowing real-time, single live-cell imaging of GR tagged with fluorescent proteins, has shown that NRs are highly mobile in the nucleus with a rapid exchange of receptor molecules on DNA, which can be measured in seconds (McNally et al., 2000; Maruvada et al., 2003; Schaaf and Cidlowski, 2003; Hager et al., 2004; Nagaich et al., 2004; Rayasam et al., 2005). Despite dynamic differences observed using both techniques, as recently discussed in Metivier et al. (2006), both methods demonstrate the highly dynamic system of transcriptional modulation mediated by NRs.

Transrepression

Evidence has accumulated over the past few years that NR action is not restricted to the positive or negative regulation of the expression of cognate target genes. Indeed, these receptors together with their mediators are targets of other major signaling cascades and reciprocally, can affect the activity of these pathways. Hence, in response to ligands, some NRs regulate gene programs not only by directly binding to HREs but also through signal transduction cross-talk, for example by interfering with AP-1 and NF-κB activities that are the prototypes of a negative regulation (Gottlicher et al., 1998; Shaulian and Karin, 2002). Mutual interference between the transcriptional activities of AP-1 and NRs has been reported, e.g., for GR, ERs, RARs, and RXRs. The importance of such cross-talk was highlighted by the observation that GR-null mice die at birth, whereas mice harboring a GR mutant that allows the separation of direct consensus glucocorticoid resoonse element-mediated transcriptional regulation from that of AP-1 transrepression are viable (Reichardt et al., 1998, 2000; Herrlich, 2001). In contrast, several reports show that under certain conditions this cross-talk can lead to positive transcriptional effects (Shemshedini et al., 1991; Bubulya et al., 1996; Pearce et al., 1998). For instance, ERα and ERβ can enhance transcription of the collagenase gene, which contains an AP-1-responsive promoter (Tan et al., 2002). Despite the proposal of several distinct mechanisms, the molecular basis of these interferences has remained elusive and requires an unknown state of the receptor (De Bosscher et al., 2001; Herrlich, 2001).

The second example of the transrepression activity of GR involves the mutual interference between GR and

NF-κB proteins that has been proved to be a major anti-inflammatory mechanism. Indeed, the agonist-bound GR physically interacts with NF-κB to block its transcriptional activity (McKay and Cidlowski, 1999; De Bosscher et al., 2003). On the other hand, agonist-bound PPARγ can antagonize inflammatory responses by transrepression of NF-κB target genes (Haffner et al., 2002). It has been recently proposed that this process involves ligand-dependent SUMOylation of the PPARγ LBD, which targets PPARγ to corepressor complexes on inflammatory gene promoters (Pascual et al., 2005). In this model gene system, receptors do not bind to DNA directly but rather physically interact with coregulators and interfere with transcription. However, as for AP-1 interference, the mechanisms of transrepression of NF-κB remain poorly understood.

Furthermore, expression of the 25-hydroxyvitamin D_3 1α-hydroxylase gene, a key enzyme in vitamin D biosynthesis, is negatively regulated by vitamin D (Takeyama et al., 1997). Recently, it has been shown that the novel ATP-dependent chromatin-remodeling complex WINAC is required for the ligand-bound VDR-mediated transrepression of this gene. In the proposed model, WINAC directly interacts with VDR (Fujiki et al., 2005). The gene is negatively regulated via recruiting chromatin remodeling and histone modification activities. In addition, NRs have been shown to affect the activities of other transcription factors such as STAT5, Oct 2A, RelA, and Spi-1/PU.1 (Hopp and Fuqua, 1998).

Post-Translational Modifications

The transcriptional activity of NRs is also modulated by various post-translational modifications of the receptors themselves or of their coregulatory proteins. Phosphorylation and several other types of modification, such as acetylation, SUMOylation, ubiquitinylation and methylation, have been reported to modulate the functions of NRs, potentially constituting an important cellular integration mechanism (Kouzarides, 2000; Wang et al., 2001a; Fu et al., 2002; Perissi and Rosenfeld, 2005). Therefore, these different modes of regulation reveal an unexpected complexity of the dynamics of NR-mediated transcription.

NRs are phosphoproteins, and multiple receptor functions can be affected by phosphorylation in response to various types of effectors (Fig. 1F). The majority of the NR phosphorylation sites lie within the amino-terminal A/B region, but phosphorylation sites are also located into both the DBD and the LBD (Rochette-Egly et al., 1995; Delmotte et al., 1999). Most of the modified residues in the A/B domain are serines surrounded by prolines and therefore correspond to consensus sites for proline-dependent kinases, which include cyclin-dependent kinases that are associated with general transcription factors, and MAPKs such as extracellular signal-regulated kinase, c-Jun NH_2-terminal kinases, and p38MAPK (Morgan, 1995; Chang and Karin, 2001; Pearson et al., 2001). Hence, such kinases, together with kinases that are activated by other signals (Akt, PKA, and PKC), cooperate with the NR ligands to enhance transcription activation. But phosphorylation can also contribute to termination of the ligand response through inducing DNA dissociation of the NR or through decreasing ligand affinity. All these modifications are exemplified by a large number of studies on RARs (Bastien and Rochette-Egly, 2004). Hence, many factors acting on kinases can modulate the response of NRs to their ligands.

Phosphorylation can also occur in the absence of ligand, and deregulation of NR phosphorylation in certain diseases or cancers may lead to apparently ligand-independent activities. Originally, steroid receptors were considered to be exclusively activated as transcription factors by binding cognate hormones. However, a wide range of extra- and intracellular signals, including a variety of growth factors, can activate the transcriptional activity of steroid receptors in the absence of their cognate ligands (reported for ER, PR, and AR) (Weigel and Zhang, 1998; Cenni and Picard, 1999; Couse and Korach, 1999; Mani, 2001).

In addition to the modifications of the receptors themselves, such modifications have been reported for their coactivators and corepressors. Indeed, SRC-1, TIF2, RAC3, PGC-1, p300, CBP, NCoR, and SMRT are phosphoproteins that are themselves targets for a variety of kinases (Font de Mora and Brown, 2000; Rowan et al., 2000; Yuan and Gambee, 2000; Knutti et al., 2001; Lopez et al., 2001; Vo and Goodman, 2001). Phosphorylation may enhance interaction of coactivators with NRs, efficiency to recruit HAT complexes, and enzymatic activity. In contrast, phosphorylation of corepressors NCoR and SMRT subsequent to the activation of MAPKs, AKT/PKB and casein kinase-2 has been shown to induce their redistribution from the nucleus to the cytoplasm and to correlate with an inhibition of their interaction with NRs (Hong and Privalsky, 2000; Zhou et al., 2001; Baek et al., 2002; Hermanson et al., 2002).

Nongenomic Effects

Another type of NR cross-talk, which has been recognized only recently, is the so-called "nongenomic" actions of several receptors that induce very rapid cellular effects (Wehling, 1997; Picard, 1998; Valverde et al., 1999; Kelly and Levin, 2001; Cato et al., 2002). Effectively, over several decades evidence has accumulated that steroid receptors may have a role that does not require their transcriptional activation, such as modifying the activity of enzymes and ion channels. Although the effects of steroids that are mediated by the modulation of gene expression do occur with a time lag of hours, steroids can induce an increase in several second messengers such as inositol triphosphate, cAMP, Ca^{2+}, and the activation of MAPK and PI3 kinase within seconds or minutes (Aronica et al., 1994; Migliaccio et al., 1996;

Improta-Brears et al., 1999; Simoncini et al., 2000). Therefore, ERs, AR, GR, and PR have been shown to couple to a large number of signaling molecules. Many mechanistic details of these nongenomic phenomena remain poorly understood. Notably, controversy still exists as to the identity of the receptors that initiate the nongenomic steroid actions. However, it now seems that at least some of the reported effects can be attributed to the same steroid receptors that are known as NRs (Migliaccio et al., 1996; Simoncini et al., 2000; Boonyaratanakornkit et al., 2001; Castoria et al., 2001; Kousteni et al., 2001). This is particularly true for some of the effects of estrogen and progesterone. However, NRs clearly do not account for all nongenomic effects elicited by steroids. There is now increasing evidence that some nongenomic actions of NR ligands are apparently mediated through membrane receptors that are not part of the NR superfamily. Indeed, several unrelated membrane receptors contribute to a large diversity of rapid responses (Wehling, 1997; Picard, 1998). In addition, the existence of binding sites for thyroid hormone on the cell surface has been known for many years (Schwartz et al., 1967; Giguere et al., 1996). A plasma membrane receptor site for the thyroid hormone on integrin $\alpha V\beta 3$, which is linked by signal-transducing MAPK (extracellular signal-regulated kinase 1/2) to cell membrane transport function and to MAPK-mediated intranuclear events, has recently been described previously (Lin et al., 2003; D'Arezzo et al., 2004; Tang et al., 2004; Bergh et al., 2005). Nonclassic modes of transcriptional regulation may need to be considered when the actions of NR ligands are evaluated.

Nuclear Receptors and Ligands

All cognate NR ligands are hydrophobic and of small size, but beyond these generalities, they vary greatly. In previous structural studies involving the conventional ligand-regulated NRs, the way in which ligands bind in the hydrophobic LBP situated within the conserved LBD and regulate NR activity has become clear. The binding selectivity is determined through specific recognition of the chemical structure of the ligand. Nevertheless, and as a result, most NRs are potentially promiscuous, as shown by the phenomenon of endocrine disruption and the generation of synthetic compounds that bind receptors with very high affinity. The role of the cognate ligand is to stabilize the AF-2 helix 12 in the active state. However, within the framework of this general mechanism, NRs have explored diverse structural mechanisms to stabilize this helix in the active conformation. In addition, NRs also include a large number of related but less well characterized orphan receptors lacking identified ligands that have raised questions about the role of ligand binding.

One of the most important mechanistic aspects that we have learned in recent years is that the response of a given tissue is dictated by the set of coregulators with which NRs interact after ligand-induced allosteric alterations that generate, expose, or remove interaction surfaces (Nagy and Schwabe, 2004). Therefore, chemistry can generate not only receptor-selective and various types of full, partial, and inverse agonists, but also molecules that activate only a subset of the functions induced by the cognate ligand or compounds that act in a cell-type-selective manner, leading to NR-based drug development (Gronemeyer et al., 2004). Overall, these findings highlight the diverse molecular mechanisms that NRs have evolved for activation.

True Orphans

A significant number of the 48 human NRs are still considered as orphan receptors as no physiologically relevant ligand has been found despite the major efforts that have been invested in finding molecules that can bind and activate these receptors. Several recent structural studies indicate that "true" orphan receptors, i.e., NRs that are not recognized by cognate endogenous ligands and in which the AF-2 helix is predisposed in the active conformation, might indeed exist. For instance, the elucidation of the 3D crystal structure of the NURR1 LBD revealed that, although this LBD is folded much the same way as in the other NRs, it lacks a cavity for ligand binding. Indeed, the LBP that is normally occupied by ligands in other classic NRs is entirely filled by hydrophobic amino acid side chains in NURR1 (Wang et al., 2003). Nevertheless, NURR1 can act as a transcription factor since target genes of this receptor have been identified. Therefore, NURR1, as well as NGFI-B, are not regulated by cognate ligands and might be regulated by alternative mechanisms. Accordingly, no known coactivators have been shown to bind to NURR1 LBD. This LBD does not harbor a conventional interacting surface for coactivator recruitment because the charge clamp present in most other NRs does not exist. Indeed, the conserved glutamate in the helix 12 is replaced by a lysine and the conserved lysine in H3 is replaced by a glutamate. However, NURR1 can recognize specific DNA-binding sites in promoters of regulated genes as monomer, homodimer, or heterodimer with the heterodimerization partner RXR (Law et al., 1992; Perlmann and Jansson, 1995; Philips et al., 1997). As a result, despite the inability to bind its own cognate ligand, NURR1 can promote signaling via its heterodimerization partner as RXR agonists can promote the survival of dopamine neurons through a process that depends on NURR1-RXR heterodimers.

Recent LBD crystal structures of the NR NR5A subfamily members have raised questions about the function of ligand binding. Surprisingly, the mouse LRH-1 LBD, which works as a monomer, exhibits a completely empty hydrophobic LBP. Although this large LBP, approximately 830 $Å^3$, does not contain a ligand, the AF-2 helix 12 is in the active conformation, generating the

hydrophobic groove required for coactivator binding. This feature can be explained by the fact that LRH-1 LBD contains a four-layer helix sandwich instead of the three-layer sandwich of other NRs. Therefore, the action of LRH-1 has been proposed to be independent of ligand (Sablin et al., 2003). But, it has been recently reported by two different laboratories that phosphoinositide phosphates and phospholipids are potential ligands of SF-1 and LRH-1 (Krylova et al., 2005; Ortlund et al., 2005). Ligand-binding seems to be required for maximal activity. On the other hand, some lipophilic molecules have been proposed to serve a structural function in constitutively active NRs, with HNF-4 binding fatty acid and RORα binding cholesterol (Dhe-Paganon et al., 2002; Kallen et al., 2002; Wisely et al., 2002). Indeed, in HNF-4, the bound palmitic acid is nonexchangeable and stabilizes the AF-2 helix in active position.

Lastly, DAX-1 and SHP, belonging to the heterogeneous NR0B group, are substantially distinct from other NRs in both structure and function. Because their three-dimensional structures have not yet been solved, it is currently unknown whether these NRs are capable of ligand binding and functioning as a conventional receptor.

The issue of cognate ligands for orphan receptors remains very controversial and unclear. Whereas a clear structural paradigm has developed to explain the activation of ligand-regulated receptors, no uniform mechanism has been proposed to account for the modulation of orphan NR activity. Nevertheless, the existence of these proteins suggests that additional unexplored NR-mediated signaling pathways remain to be characterized (Kliewer et al., 1999; Chawla et al., 2001).

Ligand-Regulated Nuclear Receptors

A remarkable diversification of the ligand selectivity of nuclear receptors has occurred since the first ligand-binding NR. Hence, NRs have evolved their affinity for one or a few specific ligands in the context of the endogenous and exogenous chemical background of the organisms of which they are a part. All NR ligands are hydrophobic, lipid-soluble, and of small size. Endogenous ligands for NRs include various cholesterol derivatives (steroid hormones, vitamin D, bile acids, and other cholesterol metabolites), retinoids, modified amino acids (thyroid hormone), prostaglandins, leukotrienes, and several fatty acids and benzoates. The hydrophobic feature of hormones and vitamins allows them to easily cross the lipid bilayer of cell membranes. Nevertheless, because of their ligand-binding ability, NRs are potentially subject to endocrine disruption by environmental pollutants. Such molecules act as NR ligands because their stereochemistry allows them to fit by chance into NR LBPs. In this respect, many plant and industrial chemicals, including pesticides, plastic components, and xenobiotic drugs, have been found to bind to and thereby mimic, block, or otherwise disrupt the natural activity of NRs (McLachlan, 2001).

The adopted orphan receptors such as PPARs, liver X receptors, and pregnane X receptor harbor a large LBP, whereas the classic receptors such as RARs and TRs contain a smaller LBP. This structural feature seems to correlate with the biology mediated by these receptors. The large pockets in adopted orphans allow these receptors to bind to diverse metabolites promiscuously and with a low affinity, highlighting a crucial role for adopted orphans as the body's lipid sensors. In contrast, the small pocket in the conventional receptors recognizes a highly specific ligand with a high affinity. Such affinity and specificity of ligand recognition may be required for these classic receptors to mediate their physiological pathways.

The role of these cognate NR ligands is to act as agonists by stabilizing the AF-2 helix 12 in the active conformation. The most straightforward mechanism is exemplified by RARs, GR, and PPARs for which the ligand directly contacts and stabilizes the helix 12 in the active conformation. In RARs and GR, this conformation is stabilized by hydrophobic interactions with the bound activating ligand (Bledsoe et al., 2002; Germain et al., 2004). In PPARs, various full agonist ligands contain an acidic head group, which forms a direct hydrogen bond with the H12 and locks this helix into the active conformation (Xu et al., 1999; Gampe et al., 2000; Cronet et al., 2001).

However, in other classic NRs, the bound agonist ligand does not make any direct contact with the AF-2 helix 12. Instead, the ligand induces a conformational change in the receptor that allows a stable docking of H12. For instance, the stabilization of H12 in the agonist conformation can be controlled by its interactions with the helix 11 as seen in the agonist-bound RXR LBD structure. In the case of ERs, agonist binding does stabilize H3 and H10, which allows the helix 12 to pack tightly against these two helices (Brzozowski et al., 1997; Shiau et al., 1998).

Ligand Specificity

In terms of ligand-binding ability, a lack of consistency in the evolution of ligands in the NR phylogeny can be observed. Steroids are able to bind to steroid receptors as well as to NRs in the distant VDR group, but the NRs that are classified in the tree between these groups are orphan receptors or bind nonsteroidal ligands. On the other hand, the two ERs, which originate from two separate genes on different chromosomes, exhibit distinct pharmacological profiles. Similarly, three paralogs exist for RAR and PPAR. However, whereas synthetic subtype-selective ligands have been generated, it remains unknown whether endogenous ligands with such specificities exist in vivo. All-*trans*-retinoic acid and estradiol can indeed activate all RAR and ER subtypes, respectively.

Crystallographic studies have revealed the structural basis of ligand recognition (Bourguet et al., 2000a; Li et al., 2003). The specificity of NR ligand-binding is determined by the shape and the volume of the LBP and the differences in amino acids that line the LBP. Steroid receptors harbor LBP volumes that are significantly larger than those of the cognate ligands. The rigidity of chair-like polycyclic structure of steroids does not allow adaptability. Hence, specificity cannot be driven by multiple hydrophobic contacts. However, the rigidity of steroids permits the establishment of stereospecific binding relationships with receptors. In other cases, the shape of the LBP matches that of the ligand, contributing to the selectivity of the LBP for the cognate ligand. Indeed, for TRβ and RARγ, the accordance of shape and volume maximizes the number of mostly hydrophobic contacts. Moreover, as shown in the case of RARs, the adaptation of ligands to the LBP leads to an optimal number of interactions for binding and selectivity.

Differences in residues that line the LBP, as well as differences in the shape of the LBP, which can greatly vary from receptor subtype to subtype, also account for most of the synthetic subtype-selective ligands that have been generated. For instance, in the case of the three RAR subtypes, sequence alignment together with the definition of residues lining the LBPs revealed only three divergent residues and LBP swaps confirmed the crucial role of these amino acids in subtype specification (Fig. 1, C and E) (Gehin et al., 1999; Germain et al., 2004). RARα and RARβ differ by just one residue in helix 3, whereas two residues located in helix 5 and helix 11 diverge in the LBPs of RARβ and RARγ. In addition, another level of specificity can be achieved. Indeed, subtype-specific differences in the shape of the pocket also allow for opposing effects of ligands on different subtypes. Differences in the PPAR subtypes allow the same ligand to lead to differential effects on corepressor recruitment, decreasing the affinity for a corepressor peptide in PPARγ but stimulating it in the other subtypes (Stanley et al., 2003). On the other hand, the mixed agonist-antagonist nature of some synthetic retinoids has been revealed. For example, BMS453 exhibits agonistic properties for RARβ and antagonistic properties for RARγ. Differences in the volume and the shape of the LBPs of these paralogs, the LBP of RARβ being significantly larger than the RARγ LBP, have been shown to account for a such mixed profile (Fig. 1D) (Germain et al., 2004).

Different Classes of Ligands

To characterize the antagonistic properties of a NR ligand, various aspects have to be considered. Indeed, antagonists may negatively affect NR activities at various levels. For instance, the stability of the complex formed between steroid receptors and heat shock protein 90 in absence of ligand can be altered or not by antagonists. The homo- or heterodimerization ability of the receptor also has to be considered. In addition, some antagonists may affect the NR interaction with its cognate DNA response element.

From a structural point of view, agonists are ligands that lock the receptor in the active conformation. In contrast, antagonists should be viewed as molecules that prevent NRs from adopting this conformation. Helix 12 is a crucial component of the NR LBDs, because its ligand-induced repositioning in the agonist-bound NR contributes in a critical manner to the surfaces recognized by the LxxLL NR boxes of coactivators and thereby generates a transcriptional active AF-2 domain. Hence, the interactions between AF-2 helix 12 or residues in its proximity and the ligand are critical for the control of agonist-antagonist properties of NRs. Several crystal structures of NR LBDs bound to antagonists have revealed that ligand interactions with helix 12 and helix 11 are primary determinants of AF-2 stability and that helix 12 not only adopt two positions, active and inactive, but can also have several intermediary positions, implying that compounds can be designed to have differing degrees of agonism or antagonism.

In addition, NRs can modulate target gene expression via two activation functions, AF-1 and AF-2, that work in a cell type- and promoter environment-dependent manner. Thus, a given antagonist may inhibit only one or both AFs, and an AF-2 antagonist can act as an AF-1 agonist. Although the structural basis of AF-1 activity is still unknown, AF-2 corresponds to agonist-induced surface that can interact with coactivators. Conversely, some unliganded NRs expose a surface that can accommodate repressors. Therefore, a given ligand may more or less precisely generate these surfaces and lead to different coregulator recruitment efficiencies.

Nuclear Receptor Antagonists

The structural determination of the ERα LBD in complexes with the selective antiestrogen raloxifene and 4-hydroxytamoxifen and of the RARα LBD-BMS614 complex provided the first structural evidence for the molecular basis of antagonism (Brzozowski et al., 1997; Shiau et al., 1998; Bourguet et al., 2000b). A general feature common to all of these antagonist molecules is the presence of a bulky side chain that cannot be accommodated within the agonist binding cavity. Together, all these structures revealed a well-conserved overall fold compared with the canonical agonist-bound NR LBD conformations. Nevertheless, because of the particular chemical structure of these antagonists, the helix 12 is unable to adopt the active position. After a clockwise rotation of ~120°, combined with a shift toward the amino terminus of the LBD, helix 12 packs on the groove formed by the carboxy terminal part of H3, L3–4, and H4. This surface also corresponds to the coactivator NR box LxxLL motif binding site. Note that helix 12 harbors conserved hydrophobic residues that define a degenerated LxxLL motif, mediating the interaction in the cleft.

From these observations, one can reason that these antagonists may prevent interaction of coactivators by inducing H12 stabilization into the hydrophobic cleft, H12 being a competitor to transcriptional coactivator association. Such antagonists can be viewed as pure AF-2 antagonists. Moreover, as the corepressor binding site on the surface of NR LBDs exhibits overlap with the coactivator recruitment site, pure AF-2 antagonists may reduce the interaction of NRs with NCoR and SMRT corepressors, as exemplified by BMS614 for RARα (Germain et al., 2002). Strikingly, the crystal structure of the antiestrogen ICI164384-bound ERβ LBD complex revealed that, in contrast to other ER antagonists, H12 cannot adopt a defined position (Pike et al., 2001). The binding of this compound to ERβ completely abolished the association between H12 and the remainder of the LBD. However, the long flexible antagonist substituent of ICI164384 may act as a competitor for coregulators because it is present in the hydrophobic groove.

Nevertheless, a number of full NR antagonists exist that do not have the bulky side chain found in the molecules discussed above. Flutamide and progesterone are potent AR and MR antagonists, respectively, although both of these ligands are similar in size to agonists for these NRs. On the other hand, an alternative mode of antagonism was suggested by the resolution of the crystal structures of ERα and ERβ in complex with THC. Interestingly, THC acts as an ERα agonist and as an ERβ antagonist. Structure comparison of the two ligand-receptor complexes reveals that THC, which lacks the bulky side chain of pure antagonists, antagonizes ERβ by stabilizing the conformation of several residue side chains from helix 11 and L11–12 in such a way that they do not create the proper hydrophobic binding surface for the active helix 12 (Shiau et al., 2002).

Inverse Agonists

Several studies of corepressor interaction and transcriptional activities revealed the existence of synthetic NR ligands, referred to as inverse agonists, which can be differentiated on the basis of their ability to inhibit NR basal transcriptional activity in the absence of exogenously added agonist. Some RAR antagonists are highly effective in inducing corepressor interaction and enhance silencing (Klein et al., 1996; Germain et al., 2002). In addition, whereas unliganded ERα does not seem to interact strongly with corepressors, it has been shown that some antagonists significantly enhance this interaction, as well as HDAC recruitment, at certain ERα target promoters (Jackson et al., 1997; Lavinsky et al., 1998; Zhang et al., 1998; Shang et al., 2000; Yamamoto et al., 2001; Shang and Brown, 2002; Webb et al., 2003). It is clear that the stable positioning of H12 either by agonists or pure AF-2 antagonists is essential for NR activation state by enhancing or reducing the affinity for the LxxLL motif of coactivator proteins, respectively, and by reducing corepressor binding. Therefore, H12 of NR LBD bound to an inverse agonist has to adopt an alternative position that does not occlude the hydrophobic groove formed by H3 and H4. In this respect, the antagonist GW6471 binding to PPARα reinforces the corepressor interaction. In contrast with other antagonist-bound NR structures, the AF-2 helix 12 undergoes a rigid body shift toward the N terminus of helix 3 and is loosely packed against this helix, leaving sufficient space to accommodate the corepressor motif (Xu et al., 2002). The third helical turn in the corepressor motif occupies the space that is left by the repositioning of helix 12 and prevents this helix from adopting its agonist-bound conformation. This structure demonstrates that H12 can be stabilized, even poorly, under the influence of a ligand in a position that is different to the well-characterized agonistic and AF-2 antagonistic conformations. Thus, the AF-2 helix may be inhibitory for full corepressor binding, and its deletion or displacement by some antagonists can potentiate the interaction.

In addition, synthetic compounds can antagonize the constitutive activity of some NRs. This phenomenon is exemplified by the activity of the synthetic estrogen DES on ERRγ (Greschik et al., 2004). Whereas DES works as a full agonist on ER, it counteracts the constitutive activity of unliganded ERRγ. The molecular mechanism of this antagonism requires the alteration of the agonist conformation of helix 11.

Partial Agonists

In addition to AF-2 pure antagonists and inverse agonists, AF-2 partial agonists-antagonists have been identified. Such compounds are potent but exhibit reduced efficacy when compared with full agonists. All structures discussed above show a strict correlation between orientation of the helix 12 and their biological activity; that is not the case for partial ligand-bound NR LBD complexes. The structure of PPARγ LBD bound to the mixed agonist-antagonist GW0072 suggests that the partial activity of this compound is attributed to poor stabilization of the agonist position of helix 12 as a result of a lack of contact between the ligand and this helix. In the presence of such mixed ligands, the equilibrium between the agonist position of H12 and its antagonist position in the coactivator binding groove is likely to depend on the intracellular concentration of coactivators and corepressors, and these ligands may act as either AF-2 agonists or antagonists depending on the cellular context. In addition, the stabilization of helix 12 in the agonist conformation is also controlled by its interaction with helix 11. As shown for other partial agonist structures, ligands such as genistein and oleic acid for ERβ and RXR, respectively, induce unwinding of helix 11 that is shifted away from helix 12, leading to a loss of stabilizing interactions and to positioning of helix 12 in the antagonist groove. Hence, these compounds can in-

duce AF-2 antagonist conformation even though they elicit a weak but clear transcriptional AF-2 activity. Overall, these observations show that partial agonist ligands display loss of interactions of helix 12 with ligand or helix 3 and helix 11, thus destabilizing the agonist conformation.

Selective Nuclear Receptor Modulators

Selective nuclear receptor modulators (SNuRMs) can also be viewed as partial agonists-antagonists. Ligands with such characteristics have been developed for a number of NRs, such as ERs (SERM), AR (selective AR modulator), and PPARs (selective PPAR modulator) (Smith and O'Malley, 2004). Their mixed agonistic-antagonistic properties are associated with differential recruitment of coactivators versus corepressors and the tissue-selective expression profiles of these coregulators (Smith et al., 1997; Liu et al., 2002; Webb et al., 2003). Such sensitivity to cell types has been demonstrated for the selective SERMs, such as raloxifene and tamoxifen, which are the prototypical examples (Shang et al., 2000). In mammary cells, both tamoxifen and raloxifene induce the recruitment of corepressors to target gene promoters. Nevertheless, in endometrial cells, tamoxifen, but not raloxifene, works like an agonist by inducing the recruitment of coactivators onto some genes. Hence, tamoxifen can also act as an agonist, presumably through coactivator interactions involving the AF-1 domain, depending on the target gene, cell, or tissue (Berry et al., 1990; Metzger et al., 1992; Mcinerney and Katzenellenbogen, 1996; Webb et al., 1998). Moreover, although the localization of helix 12 in the hydrophobic groove was originally proposed as the antagonist conformation, more recent studies suggest that this conformation may be, in fact, the SNuRM agonist conformation, allowing AF-1 activity by inhibiting corepressor recruitment to the LBD (Brzozowski et al., 1997). However, ERα bound to tamoxifen or raloxifene can recruit corepressors and a subset of HDACs at certain target promoters (Shang et al., 2000; Yamamoto et al., 2001; Shang and Brown, 2002; Webb et al., 2003). Although the action mechanism of tamoxifen as a SERM is not fully understood, the availability of coregulators has been shown to determine its transcriptional action. The estradiol-like activity of tamoxifen in the uterus requires a high level of coactivator expression (Shang and Brown, 2002). Overexpression of the coactivator SRC-1 or the corepressors NCoR and SMRT enhances or represses the partial agonist activity of tamoxifen (Jackson et al., 1997; Smith et al., 1997; Shang et al., 2000; Keeton and Brown, 2005). As a result, the overall balance and relative concentrations of coactivators and corepressors can determine the estrogenic activity of tamoxifen. In addition, it as been reported that the corepressor and coactivator expressions are responsible for the partial activity of RU486 with the PR (Liu et al., 2002). Therefore, cell type- and promoter-specific differences in coregulator recruitment determine the cellular response to SNuRMs.

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