

# International Union of Pharmacology. LXV. The Pharmacology and Classification of the Nuclear Receptor Superfamily: Glucocorticoid, Mineralocorticoid, Progesterone, and Androgen Receptors

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## Introduction

The glucocorticoid receptor (GR<sup>1</sup>), mineralocorticoid receptor (MR), progesterone receptor (PR), and androgen receptor (AR) are classic members of the nuclear receptor superfamily, composing subfamily 3C. Members of this subfamily are among those receptors that were cloned the earliest, with the GR being cloned in 1985 and the MR, PR, and AR shortly thereafter (Hollenberg et al., 1985; Arriza et al., 1987; Misrahi et al., 1987; Chang et al., 1988; Lubahn et al., 1988). Individually and in combination, these four receptors play pivotal roles in some of the most fundamental aspects of physiology such as the stress response, metabolism, immune function, electrolyte homeostasis, growth, development, and reproduction.

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<sup>1</sup> Abbreviations: GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PR, progesterone receptor; AR, androgen receptor; DBD, DNA-binding domain; LBD, ligand-binding domain; GRE, glucocorticoid response element; AF, activation function; SRC-1, steroid receptor coactivator 1; ACTH, corticotropin; CBG, corticosteroid-binding globulin; CNS, central nervous system; SHBG, sex hormone-binding globulin; HSP, heat shock protein; NCoR, nuclear receptor corepressor.

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Multiple signaling pathways have been established for all four receptors, and several common mechanisms have been revealed (Mangelsdorf et al., 1995). One main signaling pathway is via direct DNA binding and transcriptional regulation of responsive genes. Another is via protein-protein interactions, mainly with other transcription factors such as nuclear factor- $\kappa$ B, activator protein-1, or signal transducer and activator of transcription, to regulate gene expression patterns. Both pathways can up-regulate or down-regulate gene expression. Both pathways require ligand activation of the receptor and interplay with multiple protein factors such as chaperone proteins and coregulator proteins (Lonard and O'Malley, 2005).

These four steroid hormone receptors also exemplify the tremendous capacity and precision of endocrine modulatory mechanisms. Patients carrying mutated receptors frequently experience severe complications, and transgenic animals lacking individual receptors frequently cannot reproduce and/or survive (Cole et al., 1995, 2001; Lydon et al., 1995; Quigley et al., 1995; Berger et al., 1998; Tajima et al., 2000; Bray and Cotton, 2003; Sato et al., 2003; Sartorato et al., 2004; Lin et al., 2005; Matsumoto et al., 2005). Temporally controlled tissue distribution patterns during developmental stages, reproductive phases, and disease states contribute to the diverse activities of these receptors. Recently, exciting new information has emerged regarding these receptors, such as their structures, domain interactions, coregulatory part-

ners, multiple isoforms, post-translational modifications, and synthetic selective modulator ligands, which show promise for new effective therapeutic approach.

### Structure

The GR, MR, PR, and AR share structural similarities, with all containing three functional domains, i.e., the N-terminal transactivation domain followed by the DNA-binding domain (DBD) and the C-terminal ligand-binding domain (LBD) (Mangelsdorf et al., 1995). A hinge region links the DBD and the LBD. Compared with the GR, the sequence identities of the N-terminal domains of the MR, PR, and AR are 38, 24, and 16%, of the DBDs are 94, 91, and 79%, and of the LBDs are 57, 54, and 51%, respectively (Hollenberg et al., 1985; Arriza et al., 1987; Misrahi et al., 1987; Chang et al., 1988). Overall sequence identities for each receptor among different species (human, rat, and mouse) are between 81 and 97%.

The crystal structure of the DBD was solved for the GR (Luisi et al., 1991). The structures of the DBDs for other receptors can be inferred on the basis of the high degree of similarity of this domain among this group of receptors. Several unique features contribute to the ability of the GR DBD to bind specifically to its target DNA recognition sequences, termed glucocorticoid-response elements (GREs). The GR DBD has a single globular domain containing two perpendicular  $\alpha$  helices, one of which is responsible for specific DNA recognition and together with the other  $\alpha$  helix forms the cross-shaped hydrophobic core of the DBD. At the N terminus of each helix, a zinc ion coordinated by four cysteine residues in a tetrahedral geometry holds the peptide loops. The DBD, which is monomeric and unstructured in solution, dimerizes in a head-to-head orientation when it binds to DNA with the recognition helices of each DBD in adjacent major grooves of the DNA. This accounts for the cooperative binding of two DBD domains to the GRE. The precise chemistry of the protein-protein and the protein-DNA interfaces has also been elucidated (Luisi et al., 1991). The protein is anchored to the phosphate backbone with seven contacts on either side of the major groove. The DNA-recognition helix makes three van der Waals contacts between a valine and the methyl group of a thymine. Classic GREs consist of two hexameric inverted repeat half-sites separated by a 3-base pair spacer. The sequence of the half-sites determines which receptor can be recognized specifically. In nonspecific binding, the contacts made between the receptor and DNA are rearranged and fewer in number. In addition, gene-specific GR-GRE interactions have been reported. For example, it has been reported that a GR trimer binds to the pro-opiomelanocortin promoter and exerts transcription repression (Drouin et al., 1993); composite GREs recruit additional transcription factors that deter-

mine the direction of GR-mediated transcription of the proliferin gene (Diamond et al., 1990); GR forms a heterodimer with other steroid hormone receptors such as MR (Calle et al., 2003; Funder, 1993; Trapp and Holsboer, 1996) and AR (Chen et al., 1997) on some other GREs.

The crystal structures for the LBD of the GR, MR, PR, and AR have been made available through work from several groups (Williams and Sigler, 1998; Matias et al., 2000; Bledsoe et al., 2002, 2005; Kauppi et al., 2003; Fagart et al., 2005; Li et al., 2005). Remarkable similarities as well as some unique features have been identified, providing strong evidence for several important aspects of receptor function including ligand selectivity, receptor dimerization, and coactivator recruitment. One of the common features of the LBDs of the GR, MR, PR, and AR is the structural composition and organization. Each LBD contains 11  $\alpha$  helices (designated helix 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12) and four small  $\beta$  strands that fold into a three-layer helical sandwich. The region between helices 1 and 3 is unstructured in the steroid receptors, in contrast to the other nuclear receptors from which the nomenclature derives. Helices 1 and 3 form one side of the sandwich, and helices 7 and 10 form the other side. The middle layer (helices 4, 5, 8, and 9) is arranged at the upper half of the LBD, delimiting a hydrophobic cavity underneath where the steroid molecule is bound. Toward the C terminus, the activation function (AF)-2 helix, helix 12 packs against helices 3, 4, and 10 as an integrated part of the domain structure. Following helix 12 is an extended  $\beta$  strand that forms a  $\beta$  sheet together with a  $\beta$  strand between helices 8 and 9. Thus, the ligand-binding pocket has a scaffold framed by multiple helices and the first two  $\beta$  strands. The cognate steroid ligand for each receptor is completely buried within the ligand-binding pocket. Three structural features ensure ligand selectivity. First, the unique hydrogen bond network between the receptor and the bound ligand establishes specific recognition between the cognate ligand and receptor. For example, the MR ligand-binding pocket contains a unique polar surface absent in the other receptors, which is critical for specific binding of aldosterone. Second, the shape of the steroid and the topology inside the binding pocket enhance selectivity. The GR ligand-binding pocket contains a branched side pocket due to a proline residue in the linker between helices 6 and 7, which is critical for high-affinity binding of glucocorticoids to the GR. Third, the relative position of the binding pocket within the receptor LBD plays a role in ligand selectivity. Compared with the other receptors, the AR ligand-binding pocket seems to be shifted up toward helices 1 and 3, which contributes to selectivity of the AR for androgens. The relative position of the ligand-binding pocket provides a structural basis for the importance of residues outside of the pocket, which are critical for the integrity of the LBD (Rogerson et al., 1999).

Another common feature of the LBD among steroid receptors is the presence of the coactivator-binding cleft on the surface of the LBD above the ligand-binding pocket (Williams and Sigler, 1998; Matias et al., 2000; Bledsoe et al., 2002; Li et al., 2005). This AF-2 binding site is essential for the ligand-dependent recruitment of a wide variety of coactivators that determine transcriptional activity of the receptor. Specific charged residues termed charge clamps and intermolecular interactions facilitate relative cofactor selectivity by each receptor. A common motif among the coactivators that interacts with these charge clamp residues is the leucine-rich LxxLL motif (Lonard and O'Malley, 2005). The AR, however, prefers FxxLF motifs and interacts with lower binding affinity with the LxxLL-containing cofactors such as steroid receptor coactivator 1 (SRC-1) (He et al., 2002, 2004).

Structures of the N-terminal variable regions are not available to date for any of the receptors in this subfamily. Recent work from several laboratories suggests that this domain possibly folds into an organized structure and interacts with the C terminus of the receptor through specific intra- and intermolecular interactions (Langley et al., 1998; He et al., 1999; Tetel et al., 1999; Rogerson and Fuller, 2003). A glutamine-rich region in the AR N terminus is necessary and sufficient for recruiting coactivators such as SRC-1 (Bevan et al., 1999). Polymorphisms such as glutamine-rich tracts of abnormal length in the AR result in molecular changes and neurological disease (Poletti, 2004). Further work is needed to shed light on the molecular organization of this important domain that contributes to the transcriptional activity of the receptor.

### Endogenous Ligands and Their Functions

The major glucocorticoid in the human is cortisol, also called hydrocortisone, whereas in rodents the major glucocorticoid is corticosterone. The synthesis and secretion of glucocorticoids by the adrenal cortex are tightly regulated by the hypothalamo-pituitary-adrenal axis, which is sensitive to negative feedback by circulating hormones and exogenous glucocorticoids. Healthy individuals secrete 10 to 20 mg of cortisol daily (Katzung, 2004; Goodman et al., 2006). The rate of secretion follows a circadian rhythm governed by pulses of pituitary hormone corticotropin (ACTH). In plasma, cortisol is bound to circulating proteins, such as corticosteroid-binding globulin (CBG) that binds 90% of the circulating hormone under normal circumstances. The remaining cortisol is free or loosely bound to albumin and is available to exert its effects on target cells. CBG is increased in pregnancy, by estrogen administration, and in hyperthyroidism. Synthetic glucocorticoids such as dexamethasone are largely bound to albumin rather than CBG.

GR is expressed in almost all tissues although tissue- and cell cycle-specific regulation of GR levels have been

reported (Cidlowski et al., 1990; Oakley et al., 1996; Lu and Cidlowski, 2005). Glucocorticoids exert a vast array of physiological functions via the GR. Glucocorticoids are important regulators of carbohydrate, protein, and fat metabolism (Katzung, 2004; Goodman et al., 2006). In the fasting state, glucocorticoids stimulate gluconeogenesis and glycogen synthesis via a variety of mechanisms including increasing the production of enzymes critical in gluconeogenesis, stimulating the release of amino acids from muscles, promoting insulin resistance in the peripheral tissues, and inhibiting adipokines such as adiponectin. These processes protect glucose-dependent tissues such as the brain and heart during starvation. Glucocorticoids also profoundly modulate immune responses by regulating the activity of peripheral leukocytes, by suppressing the production of cytokines and chemokines, and by changing the life span of immune cells. In addition, glucocorticoids are critical for the functions of the central nervous system (CNS), digestive, hematopoietic, renal, and reproductive systems. The development of fetal lung is dependent on glucocorticoids.

The most physiologically important mineralocorticoid is aldosterone. Aldosterone is synthesized in the adrenal cortex primarily under the regulation of the renin-angiotensin system, potassium status, and ACTH. Aldosterone is secreted at the rate of 100 to 200  $\mu\text{g}/\text{day}$  in normal individuals with a moderate dietary salt intake and does not seem to be tightly bound to serum proteins (Katzung, 2004; Goodman et al., 2006). MR is expressed in epithelial tissues, such as the distal nephron or colon (Krozowski and Funder, 1983). Vectorial sodium reabsorption is driven by a mechanism coupling the apical epithelial sodium channel to sodium-potassium ATPase, the basolateral sodium pump. Both the epithelial sodium channel and  $\text{Na}^+, \text{K}^+$ -ATPase subunit genes are differentially regulated by aldosterone (Verrey et al., 1987; Kolla et al., 1999; Amasheh et al., 2000; Eppe et al., 2000; Kolla and Litwack, 2000). Consequently, aldosterone promotes the reabsorption of sodium from the distal convoluted and cortical collecting renal tubules. Sodium reabsorption in the sweat glands, salivary glands, and gastrointestinal mucosa can also be increased by aldosterone. Thus, aldosterone is a critical regulator of serum sodium and other electrolytes and of cardiovascular tone. Interestingly, MR expression and function extend to nonepithelial cells such as hippocampal and hypothalamic neurons, cardiomyocytes, the vasculature, and adipocytes, with studies reporting both physiological and pathophysiological roles of MRs at these additional sites emerging (de Kloet et al., 2000; Funder, 2004). The MR is unique in that it is the receptor for two physiological ligands, aldosterone and cortisol (or corticosterone in rodents). Both have a similar affinity for MRs and, therefore, given the much higher circulating concentration, cortisol might be expected to exclusively occupy MRs. In epithelial and vascular tissues this occupation is prevented by the presence of the

enzyme 11 $\beta$ -hydroxysteroid dehydrogenase 2, which converts cortisol to the inactive metabolite, cortisone. Inhibition of this enzyme by mutation or ingestion of inhibitors such as licorice or carbenoxolone results in inappropriate MR activation and hypertension. In other tissues such as the heart and selected areas in the CNS, the MR may act as a receptor for cortisol.

Progesterone is the most important progestin in humans. It is synthesized in the ovary, testis, and adrenal gland from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy. In the ovary, progesterone is produced primarily by the corpus luteum. In addition to having important hormonal effects, progesterone serves as a precursor in the synthesis of estrogens, androgens, and adrenocortical steroids. Normal males seem to secrete 1 to 5 mg of progesterone daily (Katzung, 2004; Goodman et al., 2006). The progesterone level is only slightly higher in the female during the follicular phase of the menstrual cycle. During the luteal phase of the cycle and in the third trimester of pregnancy, the rate of progesterone secretion increases to 10 to 20 mg/day and to several hundred milligrams during the latter part of pregnancy. In plasma, 90% or more of total progesterone is bound by albumin and CBG. PR is expressed in the female reproductive tract, mammary gland, brain, and pituitary gland (Mangal et al., 1997; Soyak et al., 2005). In many cells, estrogens induce expression of PR, and its presence is a common marker for estrogen action in both research and clinical settings. In many biological systems, progestins enhance differentiation and oppose the cell proliferation action of estrogens. The unequivocal roles of progesterone in a variety of events such as ovulation, implantation, mammary gland development, maintenance of pregnancy, and behavior are well established. Progesterone also increases the ventilatory response of the respiratory centers to carbon dioxide and decreases arterial and alveolar  $P_{CO_2}$  in the luteal phase of the menstrual cycle and during pregnancy. Progesterone has depressant and hypnotic actions in the CNS, which may be mediated via inhibitory neurotransmitter receptors. Accumulating data indicate a role for progesterone in male reproductive events (Gadkar-Sable et al., 2005).

In humans, the predominant androgen secreted by the testis is testosterone. In men, ~8 mg of testosterone is produced daily (Katzung, 2004; Goodman et al., 2006). In women, 0.25 mg of testosterone is synthesized by the ovary and by peripheral conversion of androstenedione produced by the adrenal gland. Alterations in plasma concentrations of testosterone and androstenedione occur during the menstrual cycle. In some ovarian disorders, androgens secreted by the ovary can be elevated, resulting in partial virilization. The concentration of testosterone in the plasma of males is relatively high during three periods of life: during embryonic development, during the neonatal period, and from puberty

throughout adult life. The androgen concentration starts to rise in male embryos in approximately the 8th week of development and declines before birth. Androgen rises again during the neonatal period and then falls to typical prepubertal values within the first year of life. Plasma testosterone increases again at the time of male puberty and is maintained at the adult level until it declines gradually in senescence. Approximately 40 to 65% of circulating testosterone is bound to sex hormone-binding globulin (SHBG). SHBG is increased in plasma in response to estrogen and thyroid hormone and in patients with cirrhosis of the liver. SHBG levels are decreased by androgen and growth hormone and are lower in obese individuals. Most of the remaining testosterone is bound to albumin. Approximately 2% remains free and available to enter cells and bind to intracellular AR. In AR-target tissues such as prostate and skin, testosterone is reduced at the 5 $\alpha$  position to 5-dihydrotestosterone, which serves as the active hormone (Auchus, 2004). Unlike other steroid receptors, AR is stabilized by high-affinity binding of testosterone or 5-dihydrotestosterone that induces the N-terminal FxxLF motif binding to the AF-2 in the LBD (Langley et al., 1998; He et al., 1999). 5-Dihydrotestosterone dissociates more slowly than testosterone from AR and thereby more effectively stabilizes the AR complex.

Androgens serve critical functions at different stages of life in the male (Katzung, 2004; Goodman et al., 2006). During embryonic life, androgens virilize the urogenital tract of the male embryo, and their action is thus essential for the development of the male phenotype. Lack of a fully functioning AR due to naturally occurring mutations in the male fetus results in incomplete male genital development or a female external phenotype (Quigley et al., 1995). The role of the neonatal surge of androgen secretion is not well defined, but it may contribute to developmental functions within the CNS. At puberty, androgens stimulate the development of secondary sexual characteristics. The growth-promoting properties of androgen increase height and the development of the skeletal musculature. In addition to stimulating and maintaining sexual function in men, androgens may also be responsible in part for aggressive behaviors. Androgens have critical physiological roles in women as well. Testosterone and androstenedione are precursors for estrogen biosynthesis; testosterone and 5-dihydrotestosterone also produce androgenic effects via the AR.

### Therapeutic Uses and Limitations

For several years, compounds targeting GR functions have been among the most frequently prescribed drugs. This is mainly due to immunomodulatory actions of glucocorticoids and their use in infections, allergies, eye diseases, hematological disorders, pulmonary diseases, skin diseases, inflammatory conditions of bones and joints, and acute respiratory distress syndrome (Kat-

zung, 2004; Goodman et al., 2006). In addition, glucocorticoids are a key to treating certain leukemias and are frequently included in chemotherapy regimens for their antiemetic, antiedema, and palliative properties. GR agonists are also the mainstay in the management of congenital adrenal hyperplasia and Addison's disease (adrenal insufficiency), in diagnostic tests for Cushing's syndrome (adrenal hyperfunction), and in certain psychiatric conditions. Furthermore, glucocorticoids are the treatment of choice for impending premature parturition to accelerate neonatal lung maturation. RU-486, a potent GR antagonist, causes generalized glucocorticoid resistance. In Cushing's syndrome caused by ectopic ACTH production or adrenal carcinoma, RU-486 can reverse the symptoms, ameliorate glucose intolerance, and normalize blood pressure. Multiple mechanisms contribute to the antagonistic actions of RU-486 with the GR (Rhen and Cidlowski, 2005). Binding of RU-486 with GR stabilizes the heat shock protein (HSP)-GR complex and alters the interaction of GR with coregulators, which together result in the formation of transcriptionally inactive GR molecules.

Prolonged glucocorticoid therapy causes serious side effects (Rhen and Cidlowski, 2005). Osteoporosis, metabolic syndrome, impaired development, and blunted growth all limit chronic use of glucocorticoids. Patients receiving long-term glucocorticoid treatment experience redistribution of body fat from the extremities to the trunk and face. Neural and psychological disturbances, such as psychosis, depression, and euphoria, can occur. To reduce these untoward actions of glucocorticoids, the lowest dosage with therapeutic efficacy, intermittent administration, and localized routes of administration have been implemented with some success (Buttgereit et al., 2005).

Dysregulation of the MR-aldosterone system reveals its importance in various human pathological conditions such as mineralocorticoid resistance, disorders of the CNS, hypertension, and cardiac failure (Katzung, 2004; Goodman et al., 2006). MR agonists such as fludrocortisone are used in the treatment of adrenal insufficiency. MR antagonists such as spironolactone and eplerenone are used for the treatment of hypertension, excess urine protein excretion, and heart failure. The potassium-sparing properties of spironolactone and eplerenone can be life-threatening if hyperkalemia develops (Sica, 2005).

The two most frequent uses of progestins are for contraception, either alone or with an estrogen in oral contraceptives, and for hormone replacement therapy when combined with estrogen in postmenopausal women (Katzung, 2004; Goodman et al., 2006). Progestins are also used in several settings for ovarian suppression, e.g., dysmenorrhea, endometriosis, hirsutism, and uterine bleeding. In addition, progesterone can be used diagnostically to test for estrogen secretion and for responsiveness of the endometrium. Progestins have been used as

a palliative measure for metastatic endometrial carcinoma and in the treatment of renal and breast carcinoma. The presence of the PR is considered a useful prognostic marker in breast cancer irrespective of the patient's progestational status. Contraception with progestins is useful in patients with hepatic disease, hypertension, psychosis, or mental retardation. The side effects include headache, dizziness, weight gain, and glucose intolerance. Recent studies suggest that certain progestin plus estrogen replacement regimens in postmenopausal women may increase the incidence of breast cancer, a finding that may promote the development of improved hormone replacement therapy (Rossouw et al., 2002).

The GR antagonist RU-486 is also a potent PR antagonist. RU-486 binds to PR with high affinity and can terminate pregnancy (Schreiber and Creinin, 2005). RU-486 has effects on ovulation as well. If given acutely in the mid to late follicular phase of the menstrual cycle, RU-486 delays follicle maturation and the luteinizing hormone surge, and ovulation occurs later than normal. If the drug is given intermittently or continuously, ovulation is prevented in most but not all cases. These effects are largely due to actions on the hypothalamus and pituitary rather than the ovary. RU-486 may produce effects on the cervix, myometrium, ectopic endometrial tissue (i.e., endometriosis), certain types of breast cancer, and meningiomas via its antiprogestin activity. RU-486 has been used as a postcoital contraceptive, and it may be slightly more effective than high-dose estrogen-progestin combinations. The mechanism of action in this case is thought to be prevention of implantation. Other investigational or potential uses for RU-486 include the induction of labor after fetal death or at the end of the third trimester and treatment of endometriosis, leiomyoma, breast cancer, and meningioma. The antiprogestin activity of RU-486 is mediated by binding to the PR (Wardell and Edwards, 2005). Binding of RU-486 induces a conformational change in the PR LBD that facilitates the dissociation from heat shock protein complexes, dimerization of the receptor, and cooperative binding to hormone response elements in target genes (Gass et al., 1998). The distinct conformational changes in the receptor LBD induced by RU-486 inhibit coactivator recruitment but facilitate receptor interaction with corepressors including nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid and thyroid receptors (Wagner et al., 1998). RU-486 binding to PR also disrupts an intramolecular interaction between the N and C domains that has been shown to be required for maximal activity of the agonist-occupied receptor (Tetel et al., 1999). Detailed structure-function studies have also revealed that RU-486 binding may recruit RU-486-specific corepressors to specific residues in the receptor C-terminal tail (Vegeto et al., 1992; Xu et al., 1996). In addition, RU-486-bound receptors counteract agonist-bound receptors via formation of inactive het-

erodimers (Meyer et al., 1990; Leonhardt et al., 1998). Via these mechanisms, RU-486 acts as a potent antagonist for PR. RU-486 can also be a partial agonist for both PR and GR when selective coregulators are recruited (Jackson et al., 1997; Schulz et al., 2002). Other PR antagonists such as ZK 98299 have been developed. However, none of these compounds has been used extensively in the clinical setting because of toxicity.

Androgen therapy is primarily used in male hypogonadism, in aging, and in attempts to reverse protein loss after trauma, surgery, or prolonged immobilization (Katzung, 2004; Goodman et al., 2006). Androgens are also used in boys with delayed puberty, and the weak androgen danazol is used in women with endometriosis. The principal clinical application of AR antagonists such as flutamide, nilutamide, or bicalutamide is in the treatment of prostate cancer, usually in conjunction with long-acting luteinizing hormone-releasing hormone analogs. Androgen blockade usually decreases the volume of the primary and metastatic lesions by inducing apoptosis (Kyprianou et al., 1990). Despite the initial response to antiandrogen therapy, however, an androgen-refractory status with a fatal outcome frequently develops (Isaacs, 1999). Recurrent prostate cancer seems to result from increased AR signaling caused by increased AR expression in the presence or absence of AR gene amplifications (Koivisto et al., 1997), increased expression of enzymes that convert adrenal androgens to testosterone (Stanbrough et al., 2006), AR mutations (Tan et al., 1997; Taplin et al., 1999; Marcelli et al., 2000; Feldman and Feldman, 2001; Gregory et al., 2001), or AR activation in a ligand-independent manner (Craft et al., 1999). The onset of recurrent prostate cancer seems to involve increased AR-dependent growth factor signaling that overcomes apoptosis induced by androgen depletion (Ruijter et al., 1999; Feldman and Feldman, 2001). The aim of continued research in this area is to improve the prognosis for patients with prostate cancer.

Adverse effects of androgen treatment in women include hirsutism, acne, amenorrhea, clitoral enlargement, and deepening of the voice (Katzung, 2004; Goodman et al., 2006). Androgen replacement or performance-enhancing steroid use in men may cause sleep apnea, polycythemia, azoospermia, a decrease in testicular size, aggression, and psychosis. On the other hand, androgen blockade used in treating prostate cancer can be accompanied by hot flushes, loss of libido and sexual potency, and bone loss and osteoporosis (Labrie et al., 2004).

### Prospectus

In 1849, Berthold showed that the transplantation of gonads into castrated roosters prevents the typical signs of castration and published the first experimental evidence for the effect of an endocrine gland (Klein, 1968).

More than a century later, the first steroid receptor was cloned (Hollenberg et al., 1985). In the past 20 years, tremendous progress has been made in our understanding of the fundamental mechanisms of the intracellular steroid hormone receptors. Continued effort by researchers in the field is paving the way for more efficient and specific therapeutic approaches via modulation of the GR, MR, PR, and AR. Although each of these receptors is encoded by a single gene, recent evidence suggests that multiple GR, MR, and PR receptor isoforms are produced (Kastner et al., 1990; Pascual-Le Tallec et al., 2004; Lu and Cidlowski, 2005). Via both transcriptional and translational mechanisms, the GR gene, for instance, produces a minimum of 16 GR proteins with distinct functions and tissue distribution patterns (Lu and Cidlowski, 2005). These receptor isoforms increase the number of molecular targets underlying diseases. In addition, alternative signaling pathways of steroid hormone receptors are being investigated. The ability of the GR to change the half-lives of certain mRNAs, notably via interaction with specific signals in the untranslated regions, has been recognized as a potentially important anti-inflammatory mechanism (Mozo et al., 1998; Newton et al., 1998). Steroid receptors localized on cell membranes, such as the PR on spermatozoa, can also trigger multiple signaling pathways to affect cell function (Gadkar-Sable et al., 2005). Another important aspect of continuing research is the development of selective modulators of these receptors that are capable of maintaining the beneficial responses mediated by each receptor while reducing unwanted side effects (Chang and McDonnell, 2005). For example, an ideal selective GR modulator would have therapeutic actions in specific tissues or would have the ability to dissociate transactivation and transrepression effects of GR, an ideal selective PR modulator would have antiproliferative effects on the endometrium and breast but would not oppose the protective effects of estrogen on bones and the cardiovascular system (Smith and O'Malley, 2004; Chwalisz et al., 2005), and selective AR modulators could be effective therapies in treating prostate cancer. Thus, exciting new avenues are being discovered by studies of the classic steroid hormone receptors.

Tables 1 through 4 summarize the functions, biologic activities, structural properties, and ligands of GR, MR, PR, and AR, respectively.

### REFERENCES

- Amasheh S, Epple HJ, Mankertz J, Detjen K, Goltz M, Schulzke JD, and Fromm M (2000) Differential regulation of ENaC by aldosterone in rat early and late distal colon. *Ann NY Acad Sci* **915**:92–94.
- Arriza JL, Weinberger C, Cerelli G, Glaser TM, Handelin BL, Housman DE, and Evans RM (1987) Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. *Science (Wash DC)* **237**:268–275.
- Auchus RJ (2004) The backdoor pathway to dihydrotestosterone. *Trends Endocrinol Metab* **15**:432–438.
- Berger S, Bleich M, Schmid W, Cole TJ, Peters J, Watanabe H, Kriz W, Warth R, Greger R, and Schutz G (1998) Mineralocorticoid receptor knockout mice: pathophysiology of Na<sup>+</sup> metabolism. *Proc Natl Acad Sci USA* **95**:9424–9429.
- Bevan CL, Hoare S, Claessens F, Heery DM, and Parker MG (1999) The AF1 and AF2 domains of the androgen receptor interact with distinct regions of SRC1. *Mol Cell Biol* **19**:8383–8392.

- Bledsoe RK, Madauss KP, Holt JA, Apolito CJ, Lambert MH, Pearce KH, Stanley TB, Stewart EL, Trump RP, Willson TM, et al. (2005) A ligand-mediated hydrogen bond network required for the activation of the mineralocorticoid receptor. *J Biol Chem* **280**:31283–31293.
- Bledsoe RK, Montana VG, Stanley TB, Delves CJ, Apolito CJ, McKee DD, Consler TG, Parks DJ, Stewart EL, Willson TM, et al. (2002) Crystal structure of the glucocorticoid receptor ligand binding domain reveals a novel mode of receptor dimerization and coactivator recognition. *Cell* **110**:93–105.
- Bray PJ and Cotton RG (2003) Variations of the human glucocorticoid receptor gene (NR3C1): pathological and in vitro mutations and polymorphisms. *Hum Mutat* **21**:557–568.
- Buttgereit F, Burmester GR, and Lipworth BJ (2005) Optimised glucocorticoid therapy: the sharpening of an old spear. *Lancet* **365**:801–803.
- Calle C, Campion J, Garcia-Arencibia M, Maestro B, and Davila N (2003) Transcriptional inhibition of the human insulin receptor gene by aldosterone. *J Steroid Biochem Mol Biol* **84**:543–553.
- Chang CS, Kokontis J, and Liao ST (1988) Molecular cloning of human and rat complementary DNA encoding androgen receptors. *Science (Wash DC)* **240**:324–326.
- Chang CY and McDonnell DP (2005) Androgen receptor-cofactor interactions as targets for new drug discovery. *Trends Pharmacol Sci* **26**:225–228.
- Chen S, Wang J, Yu G, Liu W, and Pearce D (1997) Androgen and glucocorticoid receptor heterodimer formation: a possible mechanism for mutual inhibition of transcriptional activity. *J Biol Chem* **272**:14087–14092.
- Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, and Elger W (2005) Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. *Endocr Rev* **26**:423–438.
- Cidlowski JA, Bellingham DL, Powell-Oliver FE, Lubahn DB, and Sar M (1990) Novel antipeptide antibodies to the human glucocorticoid receptor: recognition of multiple receptor forms in vitro and distinct localization of cytoplasmic and nuclear receptors. *Mol Endocrinol* **4**:1427–1437.
- Cole TJ, Blendy JA, Monaghan AP, Kriegstein K, Schmid W, Aguzzi A, Fantuzzi G, Hummler E, Unsicker K, and Schutz G (1995) Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. *Genes Dev* **9**:1608–1621.
- Cole TJ, Myles K, Purton JF, Brereton PS, Solomon NM, Godfrey DI, and Funder JW (2001) GRKO mice express an aberrant dexamethasone-binding glucocorticoid receptor, but are profoundly glucocorticoid resistant. *Mol Cell Endocrinol* **173**:193–202.
- Craft N, Shostak Y, Carey M, and Sawyers CL (1999) A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. *Nat Med* **5**:280–285.
- de Kloet ER, Van Acker SA, Sibug RM, Oitzl MS, Meijer OC, Rahmouni K, and de Jong W (2000) Brain mineralocorticoid receptors and centrally regulated functions. *Kidney Int* **57**:1329–1336.
- Diamond MI, Miner JN, Yoshinaga SK, and Yamamoto KR (1990) Transcription factor interactions: selectors of positive or negative regulation from a single DNA element. *Science (Wash DC)* **249**:1266–1272.
- Drouin J, Sun YL, Chamberland M, Gauthier Y, De Lean A, Nemer M, and Schmidt TJ (1993) Novel glucocorticoid receptor complex with DNA element of the hormone-repressed POMC gene. *EMBO (Eur Mol Biol Organ) J* **12**:145–156.
- Epple HJ, Amasheh S, Mankertz J, Goltz M, Schulzke JD, and Fromm M (2000) Early aldosterone effect in distal colon by transcriptional regulation of ENaC subunits. *Am J Physiol* **278**:G718–G724.
- Fagart J, Huyet J, Pinon GM, Rochel M, Mayer C, and Rafestin-Obilin ME (2005) Crystal structure of a mutant mineralocorticoid receptor responsible for hypertension. *Nat Struct Mol Biol* **12**:554–555.
- Feldman BJ and Feldman D (2001) The development of androgen-independent prostate cancer. *Nat Rev Cancer* **1**:34–45.
- Funder JW (1993) Mineralocorticoids, glucocorticoids, receptors and response elements. *Science (Wash DC)* **259**:1132–1133.
- Funder JW (2004) Is aldosterone bad for the heart? *Trends Endocrinol Metab* **15**:139–142.
- Gadkar-Sable S, Shah C, Rosario G, Sachdeva G, and Puri C (2005) Progesterone receptors: various forms and functions in reproductive tissues. *Front Biosci* **10**:2118–2130.
- Gass EK, Leonhardt SA, Nordeen SK, and Edwards DP (1998) The antagonists RU486 and ZK98299 stimulate progesterone receptor binding to deoxyribonucleic acid in vitro and in vivo, but have distinct effects on receptor conformation. *Endocrinology* **139**:1905–1919.
- Goodman LS, Gilman A, Brunton LL, Lazo JS, and Parker KL (2006) *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York.
- Gregory CW, He B, Johnson RT, Ford OH, Mohler JL, French FS, and Wilson EM (2001) A mechanism for androgen receptor-mediated prostate cancer recurrence after androgen deprivation therapy. *Cancer Res* **61**:4315–4319.
- He B, Gampe RT Jr, Kole AJ, Hnat AT, Stanley TB, An G, Stewart EL, Kalman RI, Minges JT, and Wilson EM (2004) Structural basis for androgen receptor interdomain and coactivator interactions suggests a transition in nuclear receptor activation function dominance. *Mol Cell* **16**:425–438.
- He B, Kempainen JA, Voegel JJ, Gronemeyer H, and Wilson EM (1999) Activation function 2 in the human androgen receptor ligand binding domain mediates interdomain communication with the NH<sub>2</sub>-terminal domain. *J Biol Chem* **274**:37219–37225.
- He B, Minges JT, Lee LW, and Wilson EM (2002) The FXXLF motif mediates androgen receptor-specific interactions with coregulators. *J Biol Chem* **277**:10226–10235.
- Hollenberg SM, Weinberger C, Ong ES, Cerelli G, Oro A, Lebo R, Thompson EB, Rosenfeld MG, and Evans RM (1985) Primary structure and expression of a functional human glucocorticoid receptor cDNA. *Nature (Lond)* **318**:635–641.
- Isaacs JT (1999) The biology of hormone refractory prostate cancer: why does it develop? *Urol Clin North Am* **26**:263–273.
- Jackson TA, Richer JK, Bain DL, Takimoto GS, Tung L, and Horwitz KB (1997) The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge domain-binding coactivator L7/SPA and the corepressors N-CoR or SMRT. *Mol Endocrinol* **11**:693–705.
- Kastner P, Krust A, Turcotte B, Stropp U, Tora L, Gronemeyer H, and Chambon P (1990) Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. *EMBO (Eur Mol Biol Organ) J* **9**:1603–1614.
- Katzung BG (2004) *Basic and Clinical Pharmacology*, McGraw-Hill, New York.
- Kauppi B, Jakob C, Farnegardh M, Yang J, Ahola H, Alarcon M, Calles K, Engstrom O, Harlan J, Muchmore S, et al. (2003) The three-dimensional structures of antagonistic and agonistic forms of the glucocorticoid receptor ligand-binding domain: RU-486 induces a transconformation that leads to active antagonism. *J Biol Chem* **278**:22748–22754.
- Klein M (1968) Berthold's article: transplantation of the testes (1849). *Arch Anat Histol Embryol* **51**:379–386.
- Koivisto P, Kononen J, Palmberg C, Tammela T, Hyytinen E, Isola J, Trapman J, Cleutjens K, Noordzij A, Visakorpi T, et al. (1997) Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. *Cancer Res* **57**:314–319.
- Kolla V and Litwack G (2000) Transcriptional regulation of the human Na/K ATPase via the human mineralocorticoid receptor. *Mol Cell Biochem* **204**:35–40.
- Kolla V, Robertson NM, and Litwack G (1999) Identification of a mineralocorticoid/glucocorticoid response element in the human Na/K ATPase  $\alpha$ 1 gene promoter. *Biochem Biophys Res Commun* **266**:5–14.
- Krozowski ZS and Funder JW (1983) Renal mineralocorticoid receptors and hippocampal corticosterone-binding species have identical intrinsic steroid specificity. *Proc Natl Acad Sci USA* **80**:6056–6060.
- Kyprianou N, English HF, and Isaacs JT (1990) Programmed cell death during regression of PC-82 human prostate cancer following androgen ablation. *Cancer Res* **50**:3748–3753.
- Labrie F, Cusan L, Gomez J, Luu-The V, Candas B, Belanger A, and Labrie C (2004) Major impact of hormonal therapy in localized prostate cancer—death can already be an exception. *J Steroid Biochem Mol Biol* **92**:327–344.
- Langley E, Kempainen JA, and Wilson EM (1998) Intermolecular NH<sub>2</sub>/carboxyl-terminal interactions in androgen receptor dimerization revealed by mutations that cause androgen insensitivity. *J Biol Chem* **273**:92–101.
- Leonhardt SA, Altmann M, and Edwards DP (1998) Agonist and antagonists induce homodimerization and mixed ligand heterodimerization of human progesterone receptors in vivo by a mammalian two-hybrid assay. *Mol Endocrinol* **12**:1914–1930.
- Li Y, Suino K, Daugherty J, and Xu HE (2005) Structural and biochemical mechanisms for the specificity of hormone binding and coactivator assembly by mineralocorticoid receptor. *Mol Cell* **19**:367–380.
- Lin HY, Xu Q, Yeh S, Wang RS, Sparks JD, and Chang C (2005) Insulin and leptin resistance with hyperleptinemia in mice lacking androgen receptor. *Diabetes* **54**:1717–1725.
- Lonard DM and O'Malley BW (2005) Expanding functional diversity of the coactivators. *Trends Biochem Sci* **30**:126–132.
- Lu NZ and Cidlowski JA (2005) Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. *Mol Cell* **18**:331–342.
- Lubahn DB, Joseph DR, Sullivan PM, Willard HF, French FS, and Wilson EM (1988) Cloning of human androgen receptor complementary DNA and localization to the X chromosome. *Science (Wash DC)* **240**:327–330.
- Luisi BF, Xu WX, Otwinowski Z, Freedman LP, Yamamoto KR, and Sigler PB (1991) Crystallographic analysis of the interaction of the glucocorticoid receptor with DNA. *Nature (Lond)* **352**:497–505.
- Lydon JP, DeMayo FJ, Funk CR, Mani SK, Hughes AR, Montgomery CA Jr, Shyama G, Conneely OM, and O'Malley BW (1995) Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. *Genes Dev* **9**:2266–2278.
- Mangal RK, Wiehle RD, Poindexter AN 3rd, and Weigel NL (1997) Differential expression of uterine progesterone receptor forms A and B during the menstrual cycle. *J Steroid Biochem Mol Biol* **63**:195–202.
- Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, et al. (1995) The nuclear receptor superfamily: the second decade. *Cell* **83**:835–839.
- Marcelli M, Ittmann M, Mariani S, Sutherland R, Nigam R, Murthy L, Zhao Y, DiCincin D, Puxeddu E, Esen A, et al. (2000) Androgen receptor mutations in prostate cancer. *Cancer Res* **60**:944–949.
- Matias PM, Donner P, Coelho R, Thomaz M, Peixoto C, Macedo S, Otto N, Joschko S, Scholz P, Wegg A, et al. (2000) Structural evidence for ligand specificity in the binding domain of the human androgen receptor: implications for pathogenic gene mutations. *J Biol Chem* **275**:26164–26171.
- Matsumoto T, Takeyama K, Sato T, and Kato S (2005) Study of androgen receptor functions by genetic models. *J Biochem (Tokyo)* **138**:105–110.
- Meyer ME, Pornon A, Ji JW, Bocquel MT, Chambon P, and Gronemeyer H (1990) Agonistic and antagonistic activities of RU486 on the functions of the human progesterone receptor. *EMBO (Eur Mol Biol Organ) J* **9**:3923–3932.
- Misrahi M, Atger M, d'Auriol L, Loosfelt H, Meriel C, Fridlansky F, Guiochon-Mantel A, Galibert F, and Milgrom E (1987) Complete amino acid sequence of the human progesterone receptor deduced from cloned cDNA. *Biochem Biophys Res Commun* **143**:740–748.
- Mozo L, Gayo A, Suarez A, Rivas D, Zamorano J, and Gutierrez C (1998) Glucocorticoids inhibit IL-4 and mitogen-induced IL-4R $\alpha$  chain expression by different posttranscriptional mechanisms. *J Allergy Clin Immunol* **102**:968–976.
- Newton R, Seybold J, Kuitert LM, Bergmann M, and Barnes PJ (1998) Repression of cyclooxygenase-2 and prostaglandin E<sub>2</sub> release by dexamethasone occurs by transcriptional and post-transcriptional mechanisms involving loss of polyadenylated mRNA. *J Biol Chem* **273**:32312–32321.
- Oakley RH, Sar M, and Cidlowski JA (1996) The human glucocorticoid receptor beta

- isoform: expression, biochemical properties, and putative function. *J Biol Chem* **271**:9550–9559.
- Pascual-Le Tallec L, Demange C, and Lombes M (2004) Human mineralocorticoid receptor A and B protein forms produced by alternative translation sites display different transcriptional activities. *Eur J Endocrinol* **150**:585–590.
- Poletti A (2004) The polyglutamine tract of androgen receptor: from functions to dysfunctions in motor neurons. *Front Neuroendocrinol* **25**:1–26.
- Quigley CA, De Bellis A, Marschke KB, el-Awady MK, Wilson EM, and French FS (1995) Androgen receptor defects: historical, clinical, and molecular perspectives. *Endocr Rev* **16**:271–321.
- Rhen T and Cidlowski JA (2005) Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med* **353**:1711–1723.
- Rogerson FM, Dimopoulos N, Sluka P, Chu S, Curtis AJ, and Fuller PJ (1999) Structural determinants of aldosterone binding selectivity in the mineralocorticoid receptor. *J Biol Chem* **274**:36305–36311.
- Rogerson FM and Fuller PJ (2003) Interdomain interactions in the mineralocorticoid receptor. *Mol Cell Endocrinol* **200**:45–55.
- Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, et al. (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *J Am Med Assoc* **288**:321–333.
- Ruijter E, van de Kaa C, Miller G, Ruiters D, Debruyne F, and Schalken J (1999) Molecular genetics and epidemiology of prostate carcinoma. *Endocr Rev* **20**:22–45.
- Sartorato P, Cluzeaud F, Fagart J, Viengchareun S, Lombes M, and Zennaro MC (2004) New naturally occurring missense mutations of the human mineralocorticoid receptor disclose important residues involved in dynamic interactions with deoxyribonucleic acid, intracellular trafficking, and ligand binding. *Mol Endocrinol* **18**:2151–2165.
- Sato T, Matsumoto T, Yamada T, Watanabe T, Kawano H, and Kato S (2003) Late onset of obesity in male androgen receptor-deficient (AR KO) mice. *Biochem Biophys Res Commun* **300**:167–171.
- Schreiber C and Creinin M (2005) Mifepristone in abortion care. *Semin Reprod Med* **23**:82–91.
- Schulz M, Eggert M, Baniahmad A, Dostert A, Heinzel T, and Renkawitz R (2002) RU486-induced glucocorticoid receptor agonism is controlled by the receptor N terminus and by corepressor binding. *J Biol Chem* **277**:26238–26243.
- Sica DA (2005) The risks and benefits of aldosterone antagonists. *Curr Heart Fail Rep* **2**:65–71.
- Smith CL and O'Malley BW (2004) Coregulator function: a key to understanding tissue specificity of selective receptor modulators. *Endocr Rev* **25**:45–71.
- Soyal SM, Mukherjee A, Lee KY, Li J, Li H, DeMayo FJ, and Lydon JP (2005) Cre-mediated recombination in cell lineages that express the progesterone receptor. *Genesis* **41**:58–66.
- Stanbrough M, Bubley GJ, Ross K, Golub TR, Rubin MA, Penning TM, Febbo PG, and Balk SP (2006) Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Res* **66**:2815–2825.
- Tajima T, Kitagawa H, Yokoya S, Tachibana K, Adachi M, Nakae J, Suwa S, Katoh S, and Fujieda K (2000) A novel missense mutation of mineralocorticoid receptor gene in one Japanese family with a renal form of pseudohypoaldosteronism type 1. *J Clin Endocrinol Metab* **85**:4690–4694.
- Tan J, Sharief Y, Hamil KG, Gregory CW, Zang DY, Sar M, Gumerlock PH, DeVere White RW, Pretlow TG, Harris SE, et al. (1997) Dehydroepiandrosterone activates mutant androgen receptors expressed in the androgen-dependent human prostate cancer xenograft CWR22 and LNCaP cells. *Mol Endocrinol* **11**:450–459.
- Taplin ME, Bubley GJ, Ko YJ, Small EJ, Upton M, Rajeshkumar B, and Balk SP (1999) Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. *Cancer Res* **59**:2511–2515.
- Tetel MJ, Giangrande PH, Leonhardt SA, McDonnell DP, and Edwards DP (1999) Hormone-dependent interaction between the amino- and carboxyl-terminal domains of progesterone receptor in vitro and in vivo. *Mol Endocrinol* **13**:910–924.
- Trapp T and Holsboer F (1996) Heterodimerization between mineralocorticoid and glucocorticoid receptors increases the functional diversity of corticosteroid action. *Trends Pharmacol Sci* **17**:145–149.
- Vegeto E, Allan GF, Schrader WT, Tsai MJ, McDonnell DP, and O'Malley BW (1992) The mechanism of RU486 antagonism is dependent on the conformation of the carboxy-terminal tail of the human progesterone receptor. *Cell* **69**:703–713.
- Verrey F, Schaerer E, Zoerkler P, Paccolat MP, Geering K, Kraehenbuhl JP, and Rossier BC (1987) Regulation by aldosterone of Na<sup>+</sup>,K<sup>+</sup>-ATPase mRNAs, protein synthesis, and sodium transport in cultured kidney cells. *J Cell Biol* **104**:1231–1237.
- Wagner BL, Norris JD, Knotts TA, Weigel NL, and McDonnell DP (1998) The nuclear corepressors NCoR and SMRT are key regulators of both ligand- and 8-bromo-cyclic AMP-dependent transcriptional activity of the human progesterone receptor. *Mol Cell Biol* **18**:1369–1378.
- Wardell SE and Edwards DP (2005) Mechanisms controlling agonist and antagonist potential of selective progesterone receptor modulators (SPRMs). *Semin Reprod Med* **23**:9–21.
- Williams SP and Sigler PB (1998) Atomic structure of progesterone complexed with its receptor. *Nature (Lond)* **393**:392–396.
- Xu J, Nawaz Z, Tsai SY, Tsai MJ, and O'Malley BW (1996) The extreme C terminus of progesterone receptor contains a transcriptional repressor domain that functions through a putative corepressor. *Proc Natl Acad Sci USA* **93**:12195–12199.

TABLE 1  
GR

Receptor nomenclature	NR3C1
Receptor code	4.10.1.GC:3:C1
Other names	GCCR, GCR, GRL
Molecular information	Hs: 777aa, P04150, chr. 5q31-q32 <sup>1</sup> Rn: 795aa, P06536, chr. 18p12 <sup>2</sup> Mm: 783aa, P06537, chr. 18 B3 <sup>3</sup>
DNA binding	
Structure	Homodimer
HRE core sequence	GGTACANNNTGTTCT (GRE, half-site, palindrome)
Partners	HSP90 (physical, functional): cellular localization <sup>4-6</sup> ; HMGB (physical, functional): DNA binding <sup>7,8</sup> ; AP-1 (physical, functional): transactivation <sup>9-11</sup> ; NF-κB (physical, functional): transactivation <sup>12,13</sup> ; 14-3-3σ (physical, functional): cellular localization, transactivation <sup>14</sup>
Agonists	Dexamethasone (1–8 nM),* triamcinolone acetonide (6 nM),* prednisolone (15 nM), triamcinolone (20 nM), cortisol (10–50 nM),* corticosterone (60 nM),* desoxycorticosterone (70 nM) [IC <sub>50</sub> ] <sup>15-19</sup>
Antagonists	RU-486 (0.4 nM)* [K <sub>d</sub> ] <sup>15,20</sup>
Coactivator	CREBBP, NCOA2, MTI-II, NCOA6, PPARBP <sup>22-27</sup>
Corepressor	BAG1 <sup>28</sup>
Biologically important isoforms	GRα {Hs, Mm, Rn}: main isoform <sup>1</sup> ; GRβ {Hs}: widely expressed alternative splicing variant lacking ligand binding, associated with several diseases <sup>1,29</sup> ; GR-A, B, C, D {Hs, Mm, Rn}: alternative translation initiation isoforms with distinct transcriptional activities and tissue distribution patterns <sup>30</sup>
Tissue distribution	Ubiquitous {Hs, Mm, Rn} [Northern blot, Q-PCR, in situ hybridization, Western blot] <sup>1,30-33</sup>
Functional assay	Suppression of endogenous cortisol level by exogenous dexamethasone {Hs} <sup>34</sup> ; apoptosis of thymocytes in the thymus {Rn} <sup>35</sup> ; elevated blood glucose level by intravenous injection of glucocorticoids {Hs} <sup>36,37</sup>
Main target genes	Activated: PEPCK-C {Hs}, <sup>38</sup> MKP-1 {Mm}, <sup>39</sup> lipocortin-1 {Hs}, <sup>40,41</sup> ; repressed: PEPCK-C {Hs}, <sup>38</sup> IL-8 {Hs}, <sup>42</sup> TNF-α {Hs} <sup>43</sup>
Mutant phenotype	GR <sup>-/-</sup> mice die within hours because of respiratory failure; they have atelectatic lungs, impaired liver function, impaired HPA axis, increased plasma levels of ACTH and corticosterone and enlarged adrenal glands that produce no adrenaline {Mm} [knockout] <sup>44,45</sup> ; mice expressing type II GR antisense RNA exhibit impaired T-cell function, disrupted HPA axis, increased plasma levels of ACTH and corticosterone, reduced GR binding, and alterations in thymocyte migration {Mm} [antisense oligonucleotide] <sup>46</sup>
Human disease	Glucocorticoid resistance: due to various SNPs <sup>47,48</sup> ; glucocorticoid hypersensitivity: due to an N363 polymorphism <sup>49</sup> ; asthma: due to a receptor mutation <sup>50,51</sup> ; acute childhood lymphoblastic leukemia: due to a receptor mutation <sup>52</sup>

aa, amino acids; chr., chromosome; HRE, hormone response element; RXR, retinoid X receptor; HMGB, chromosomal high-mobility group B; NK-κ B, nuclear factor-κ B; PPARBP, peroxisome proliferator-activated receptor binding protein; Q-PCR, quantitative polymerase chain reaction; HPA, hypothalamo-pituitary-adrenal; ACTH, adrenocorticotropic; SNP, single-nucleotide polymorphism; GRE, glucocorticoid response element; CREBBP, cAMP response element binding protein binding protein.

\* Radioligand.

- Hollenberg SM, Weinberger C, Ong ES, Cerelli G, Oro A, Lebo R, Thompson EB, Rosenfeld MG, and Evans RM (1985) Primary structure and expression of a functional human glucocorticoid receptor cDNA. *Nature (Lond)* **318**:635–641.
- Miesfeld R, Rusconi S, Godowski PJ, Maler BA, Okret S, Wikstrom AC, Gustafsson JA, and Yamamoto KR (1986) Genetic complementation of a glucocorticoid receptor deficiency by expression of cloned receptor cDNA. *Cell* **46**:389–399.
- Danielsen M, Northrop JP, and Ringold GM (1986) The mouse glucocorticoid receptor: mapping of functional domains by cloning, sequencing and expression of wild-type and mutant receptor proteins. *EMBO (Eur Mol Biol Organ) J* **5**:2513–2522.
- Pratt WB (1993) The role of heat shock proteins in regulating the function, folding, and trafficking of the glucocorticoid receptor. *J Biol Chem* **268**:21455–21458.
- Pratt WB and Toft DO (1997) Steroid receptor interactions with heat shock protein and immunophilin chaperones. *Endocr Rev* **18**:306–360.
- Pratt WB, Galigniana MD, Morishima Y, and Murphy PJ (2004) Role of molecular chaperones in steroid receptor action. *Essays Biochem* **40**:41–58.
- Boonyaratankornkit V, Melvin V, Prendergast P, Altmann M, Ronfani L, Bianchi ME, Taraseviciene L, Nordeen SK, Allegretto EA, and Edwards DP (1998) High-mobility group chromatin proteins 1 and 2 functionally interact with steroid hormone receptors to enhance their DNA binding in vitro and transcriptional activity in mammalian cells. *Mol Cell Biol* **18**:4471–4487.
- Verrijdt G, Haeleens A, Schoenmakers E, Rombauts W, and Claessens F (2002) Comparative analysis of the influence of the high-mobility group box 1 protein on DNA binding and transcriptional activation by the androgen, glucocorticoid, progesterone and mineralocorticoid receptors. *Biochem J* **361**:97–103.
- Yang-Yen HF, Chambard JC, Sun YL, Smeal T, Schmidt TJ, Drouin J, and Karin M (1990) Transcriptional interference between c-Jun and the glucocorticoid receptor: mutual inhibition of DNA binding due to direct protein-protein interaction. *Cell* **62**:1205–1215.
- Schule R, Rangarajan P, Kliewer S, Ransone LJ, Bolado J, Yang N, Verma IM, and Evans RM (1990) Functional antagonism between oncoprotein c-Jun and the glucocorticoid receptor. *Cell* **62**:1217–1226.
- Jonat C, Rahmsdorf HJ, Park KK, Cato AC, Gebel S, Ponta H, and Herrlich P (1990) Antitumor promotion and antiinflammation: down-modulation of AP-1 (Fos/Jun) activity by glucocorticoid hormone. *Cell* **62**:1189–1204.
- Caldenhoven E, Liden J, Wissink S, Van de Stolpe A, Raaijmakers J, Koenderman L, Okret S, Gustafsson JA, and Van der Saag PT (1995) Negative cross-talk between RelA and the glucocorticoid receptor: a possible mechanism for the antiinflammatory action of glucocorticoids. *Mol Endocrinol* **9**:401–412.
- Scheinman RI, Gualberto A, Jewell CM, Cidlowski JA, and Baldwin AS Jr (1995) Characterization of mechanisms involved in transrepression of NF-κ B by activated glucocorticoid receptors. *Mol Cell Biol* **15**:943–953.
- Kino T, Souvatzoglou E, De Martino MU, Tsopanomihalu M, Wan Y, and Chrousos GP (2003) Protein 143-3σ interacts with and favors cytoplasmic subcellular localization of the glucocorticoid receptor, acting as a negative regulator of the glucocorticoid signaling pathway. *J Biol Chem* **278**:25651–25656.
- Rupprecht R, Reul JM, van Steensel B, Spengler D, Soder M, Berning B, Holsboer F, and Damm K (1993) Pharmacological and functional characterization of human mineralocorticoid and glucocorticoid receptor ligands. *Eur J Pharmacol* **247**:145–154.
- Hellal-Levy C, Couette B, Fagart J, Souque A, Gomez-Sanchez C, and Rafestin-Oblin M (1999) Specific hydroxylations determine selective corticosteroid recognition by human glucocorticoid and mineralocorticoid receptors. *FEBS Lett* **464**:9–13.
- Lind U, Greenidge P, Gillner M, Koehler KF, Wright A, and Carlstedt-Duke J (2000) Functional probing of the human glucocorticoid receptor steroid-interacting surface by site-directed mutagenesis: Gln-642 plays an important role in steroid recognition and binding. *J Biol Chem* **275**:19041–19049.
- Giannopoulos G and Keichline D (1981) Species-related differences in steroid-binding specificity of glucocorticoid receptors in lung. *Endocrinology* **108**:1414–1419.

19. Yoneda Y, Han D, Ogita K, and Watanabe A (1995) Distinction between binding of [<sup>3</sup>H]triamcinolone acetonide to a ligand binding domain on the glucocorticoid receptor complex in cytosol fractions of brain and liver from the rat with intact adrenals. *Brain Res* **685**:105–116.
20. Heikinheimo O, Kontula K, Croxatto H, Spitz I, Luukkainen T, and Lahteenmaki P (1987) Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. *J Steroid Biochem* **26**:279–284.
21. Kamei Y, Xu L, Heinzel T, Torchia J, Kurokawa R, Glass B, Lin SC, Heyman RA, Rose DW, Glass CK, et al. (1996) A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. *Cell* **85**:403–414.
22. Hong H, Kohli K, Trivedi A, Johnson DL, and Stallcup MR (1996) GRIP1, a novel mouse protein that serves as a transcriptional coactivator in yeast for the hormone binding domains of steroid receptors. *Proc Natl Acad Sci USA* **93**:4948–4952.
23. Voegel JJ, Heine MJ, Zechel C, Chambon P, and Gronemeyer H (1996) TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. *EMBO (Eur Mol Biol Organ) J* **15**:3667–3675.
24. Torchia J, Rose DW, Inostroza J, Kamei Y, Westin S, Glass CK, and Rosenfeld MG (1997) The transcriptional co-activator p/CIP binds CBP and mediates nuclear-receptor function. *Nature (Lond)* **387**:677–684.
25. Okamoto K and Isohashi F (2005) Macromolecular-translocation inhibitor-II (Zn<sup>2+</sup>-binding protein, parathymosin) interacts with the glucocorticoid receptor and enhances transcription in vivo. *J Biol Chem* **280**:36986–36993.
26. Lee SK, Anzick SL, Choi JE, Bubendorf L, Guan XY, Jung YK, Kallioniemi OP, Kononen J, Trent JM, Azorsa D, et al. (1999) A nuclear factor, ASC-2, as a cancer-amplified transcriptional coactivator essential for ligand-dependent transactivation by nuclear receptors in vivo. *J Biol Chem* **274**:34283–34293.
27. Rachez C, Lemon BD, Suldan Z, Bromleigh V, Gamble M, Naar AM, Erdjument-Bromage H, Tempst P, and Freedman LP (1999) Ligand-dependent transcription activation by nuclear receptors requires the DRIP complex. *Nature (Lond)* **398**:824–828.
28. Kullmann M, Schneikert J, Moll J, Heck S, Zeiner M, Gehring U, and Cato AC (1998) RAP46 is a negative regulator of glucocorticoid receptor action and hormone-induced apoptosis. *J Biol Chem* **273**:14620–14625.
29. Schaaf MJ and Cidlowski JA (2002) The glucocorticoid receptor  $\beta$ -isoform: a perspective on its relevance in human health and disease. *Ernst Schering Res Found Workshop* **197**–211.
30. Lu NZ and Cidlowski JA (2005) Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. *Mol Cell* **18**:331–342.
31. Cidlowski JA, Bellingham DL, Powell-Oliver FE, Lubahn DB, and Sar M (1990) Novel antipeptide antibodies to the human glucocorticoid receptor: recognition of multiple receptor forms in vitro and distinct localization of cytoplasmic and nuclear receptors. *Mol Endocrinol* **4**:1427–1437.
32. Oakley R. H., Sar, M., and Cidlowski, J. A. (1996) The human glucocorticoid receptor  $\beta$  isoform: expression, biochemical properties, and putative function. *J Biol Chem* **271**:9550–9559.
33. Oakley RH, Webster JC, Sar M, Parker CR Jr, and Cidlowski JA (1997) Expression and subcellular distribution of the  $\beta$ -isoform of the human glucocorticoid receptor. *Endocrinology* **138**:5028–5038.
34. Jerjes WK, Cleare AJ, Wood PJ, and Taylor NF (2006) Assessment of subtle changes in glucocorticoid negative feedback using prednisolone: comparison of salivary free cortisol and urinary cortisol metabolites as endpoints. *Clin Chim Acta* **364**:279–286
35. Cidlowski JA and Munck A (1976) Concanavalin A-induced glucocorticoid resistance in rat thymus cells: decreased cytoplasmic and nuclear receptor binding of dexamethasone. *J Steroid Biochem* **7**:1141–1145.
36. West KM (1959) Response of the blood glucose to glucocorticoids in man; determination of the hyperglycemic potencies of glucocorticoids. *Diabetes* **8**:22–28.
37. Segal HL and Gonzalezlopez C (1963) Early effects of glucocorticoids on precursor incorporation into glycogen. *Nature (Lond)* **200**:143–144.
38. Cassuto H, Kochan K, Chakravarty K, Cohen H, Blum B, Olswang Y, Hakimi P, Xu C, Massillon D, Hanson RW, et al. (2005) Glucocorticoids regulate transcription of the gene for phosphoenolpyruvate carboxykinase (GTP) in the liver via an extended glucocorticoid regulatory unit. *J Biol Chem* **280**:33873–33884.
39. Kassel O, Sancono A, Kratzschmar J, Kreft B, Stassen M, and Cato AC (2001) Glucocorticoids inhibit MAP kinase via increased expression and decreased degradation of MKP-1. *EMBO (Eur Mol Biol Organ) J* **20**:7108–7116.
40. Rothhut B, Cloix JF, and Russo-Marie F (1983) Dexamethasone induces the synthesis of 'renocortins,' two antiphospholipase proteins in rat renomedullary interstitial cells in culture. *Adv Prostaglandin Thromboxane Leukotriene Res* **12**:51–56.
41. Mitchell MD, Lytton FD, and Varticovski L (1988) Paradoxical stimulation of both lipocortin and prostaglandin production in human amnion cells by dexamethasone. *Biochem Biophys Res Commun* **151**:137–141.
42. Tobler A, Meier R, Seitz M, Dewald B, Baggiolini M, and Fey MF (1992) Glucocorticoids downregulate gene expression of GM-CSF, NAP-1/IL-8, and IL-6, but not of M-CSF in human fibroblasts. *Blood* **79**:45–51.
43. Waage A (1987) Production and clearance of tumor necrosis factor in rats exposed to endotoxin and dexamethasone. *Clin Immunol Immunopathol* **45**:348–355.
44. Cole TJ, Blendy JA, Monaghan AP, Kriegstein K, Schmid W, Aguzzi A, Fantuzzi G, Hummler E, Unsicker K, and Schutz G (1995) Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. *Genes Dev* **9**:1608–1621.
45. Cole TJ, Myles K, Purton JF, Brereton PS, Solomon NM, Godfrey DI, and Funder JW (2001) GRKO mice express an aberrant dexamethasone-binding glucocorticoid receptor, but are profoundly glucocorticoid resistant. *Mol Cell Endocrinol* **173**:193–202.
46. Morale MC, Batticane N, Gallo F, Barden N, and Marchetti B (1995) Disruption of hypothalamic-pituitary-adrenocortical system in transgenic mice expressing type II glucocorticoid receptor antisense ribonucleic acid permanently impairs T cell function: effects on T cell trafficking and T cell responsiveness during postnatal development. *Endocrinology* **136**:3949–3960.
47. Bray PJ and Cotton RG (2003) Variations of the human glucocorticoid receptor gene (NR3C1): pathological and in vitro mutations and polymorphisms. *Hum Mutat* **21**:557–568.
48. Bronnegard M, Stierna P, and Marcus C (1996) Glucocorticoid resistant syndromes—molecular basis and clinical presentations. *J Neuroendocrinol* **8**:405–415.
49. Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, Grobbee DE, Brinkmann AO, De Jong FH, and Lamberts SW (1998) A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. *J Clin Endocrinol Metab* **83**:144–151.
50. Corrigan CJ, Brown PH, Barnes NC, Szefer SJ, Tsai JJ, et al. (1991) Glucocorticoid resistance in chronic asthma: Glucocorticoid pharmacokinetics, glucocorticoid receptor characteristics, and inhibition of peripheral blood T cell proliferation by glucocorticoids in vitro. *Am Rev Respir Dis* **144**:1016–1025.
51. Barnes PJ, Greening AP, and Crompton GK (1995) Glucocorticoid resistance in asthma. *Am J Respir Crit Care Med* **152**:S125–S140.
52. Haarman EG, Kaspers GJ, Pieters R, Rottier MM, and Veerman AJ (2004) Glucocorticoid receptor  $\alpha$ ,  $\beta$  and  $\gamma$  expression vs in vitro glucocorticoid resistance in childhood leukemia. *Leukemia* **18**:530–537.

TABLE 2  
MR

Receptor nomenclature	NR3C2
Receptor code	4.10.1:MC:3:C2
Other names	MR, MCR, MLR, aldosterone receptor
Molecular information	Hs: 984aa, P08235, chr. 4q31.1 <sup>1</sup> Rn: 981aa, P22199, chr. 19q11 <sup>2</sup> Mm: 978aa, Q8VII8, chr. 8 C1 <sup>3</sup>
DNA binding	
Structure	Homodimer, heterodimer
HRE core sequence	ACAAGANNNTGTTCT (GRE, half-site, palindrome)
Partners	HSP90 (physical, functional): cellular localization <sup>4</sup> ; HMGB (physical, functional): DNA binding <sup>5,6</sup> ; 11 $\beta$ -HSD2 (functional): tissue specificity <sup>7</sup>
Agonists	Desoxycorticosterone ( $1 \times 10^{-11}$ M), progesterone ( $1 \times 10^{-11}$ M),* fludrocortisone ( $1.2 \times 10^{-10}$ M), cortisol ( $1.1-1.5 \times 10^{-10}$ M), dexamethasone ( $1 \times 10^{-9}$ M)* [IC <sub>50</sub> ] <sup>8,9</sup> ; aldosterone ( $1-1.5 \times 10^{-10}$ )* [K <sub>d</sub> ] <sup>8,9</sup>
Antagonists	Drospirenone ( $<1 \times 10^{-10}$ M), spironolactone ( $1.4 \times 10^{-8}$ M), eplerenone ( $1 \times 10^{-7}$ M) [IC <sub>50</sub> ] <sup>8,10-12</sup>
Coactivator	NCOA1, PGC-1 $\alpha$ , ELL <sup>13-15</sup>
Corepressor	NCOR1, NCOR2, PIAS1 <sup>16,17</sup>
Biologically important isoforms	MR-A (Hs, Mm, Rn): main isoform <sup>18</sup> ; MR-B (Hs, Mm, Rn): truncated N terminus <sup>18</sup> ; various splice variants also exist resulting in either altered DNA or ligand binding (Hs, Rn) <sup>19-21</sup>
Tissue distribution	Liver, brain, heart, kidney, colon, aorta, hippocampus, hypothalamus, adrenal fasciculate, epidermal keratinocytes, neurons of the CNS, cardiac myocytes, endothelial and smooth muscle cells of the vasculature {Hs,Mm,Rn} [Northern blot, Q-PCR, in situ hybridization, Western blot, immunohistology] <sup>22-33</sup>
Functional assay	Renal clearance {Mm} <sup>34</sup> ; colonic transepithelial Na <sup>+</sup> reabsorption {Mm} <sup>34,35</sup>
Main target genes	Activated: Enac {Hs}, <sup>36,37</sup> SGK1{Rn}, <sup>38-40</sup> GILZ{Rn} <sup>41</sup>
Mutant phenotype	Homozygous MR-deficient mice have a normal prenatal development; during the 1st week of life, these animals develop symptoms of pseudohypoaldosteronism, lose weight, and eventually die at around day 10 due to kidney failure {Mm} [knockout] <sup>34</sup> ; a conditional knockout model expressing solely in the heart an antisense mRNA directed against the murine MR; within 2-3 months, mice develop severe heart failure in the absence of hypertension or chronic hyperaldosteronism {Mm} [antisense oligonucleotide] <sup>3</sup>
Human disease	Hypertension: Ser <sup>810</sup> $\rightarrow$ Ile SNP causes gain of function <sup>42</sup> ; pseudohypoaldosteronism type 1: various polymorphisms cause loss of activity; autosomal-dominant; haploinsufficiency seems to be the predominant mechanism <sup>43,44</sup>

aa, amino acids; chr., chromosome; HRE, hormone response element; ELL, eleven-nineteen lysine-rich leukemia; HMGB, chromosomal high-mobility group B; 11 $\beta$ -HSD2, 11 $\beta$ -hydroxysteroid dehydrogenase 2; Q-PCR, quantitative polymerase chain reaction; SNP, single-nucleotide polymorphism; GRE, glucocorticoid response element.

\* Radioligand.

1. Arriza JL, Weinberger C, Cerelli G, Glaser TM, Handelin BL, Housman DE, and Evans RM (1987) Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. *Science (Wash DC)* **237**:268-275.
2. Patel PD, Sherman TG, Goldman DJ, and Watson SJ (1989) Molecular cloning of a mineralocorticoid (type I) receptor complementary DNA from rat hippocampus. *Mol Endocrinol* **3**:1877-1885.
3. Beggah AT, Escoubet B, Puttini S, Cailmail S, Delage V, Ouvrard-Pascaud A, Bocchi B, Peuchmaur M, Delcayre C, Farman N, et al. (2002) Reversible cardiac fibrosis and heart failure induced by conditional expression of an antisense mRNA of the mineralocorticoid receptor in cardiomyocytes. *Proc Natl Acad Sci USA* **99**:7160-7165.
4. Pratt WB, Galigniana MD, Morishima Y, and Murphy PJ (2004) Role of molecular chaperones in steroid receptor action. *Essays Biochem* **40**:41-58.
5. Boonyaratankornkit V, Melvin V, Prendergast P, Altmann M, Ronfani L, Bianchi ME, Tarasevicene L, Nordeen SK, Allegretto EA, and Edwards DP (1998) High-mobility group chromatin proteins 1 and 2 functionally interact with steroid hormone receptors to enhance their DNA binding in vitro and transcriptional activity in mammalian cells. *Mol Cell Biol* **18**:4471-4487.
6. Verrijdt G, Haelens A, Schoenmakers E, Rombauts W, and Claessens F (2002) Comparative analysis of the influence of the high-mobility group box 1 protein on DNA binding and transcriptional activation by the androgen, glucocorticoid, progesterone and mineralocorticoid receptors. *Biochem J* **361**:97-103.
7. Farman N and Rafestin-Oblin ME (2001) Multiple aspects of mineralocorticoid selectivity. *Am J Physiol* **280**:F181-F192.
8. Rupperecht R, Reul JM, van Steensel B, Spengler D, Soder M, Berning B, Holsboer F, and Damm K (1993) Pharmacological and functional characterization of human mineralocorticoid and glucocorticoid receptor ligands. *Eur J Pharmacol* **247**:145-154.
9. Hella-Levy C, Couette B, Fagart J, Souque A, Gomez-Sanchez C, and Rafestin-Oblin M (1999) Specific hydroxylations determine selective corticosteroid recognition by human glucocorticoid and mineralocorticoid receptors. *FEBS Lett* **464**:9-13.
10. Pollow K, Juchem M, Elger W, Jacobi N, Hoffmann G, and Mobus V (1992) Dihydrospirorenone (ZK30595): a novel synthetic progestagen—characterization of binding to different receptor proteins. *Contraception* **46**:561-574.
11. de Gasparo M, Joss U, Ramjoue HP, Whitebread SE, Haenni H, Schenkel L, Kraehenbuehl C, Biollaz M, Grob J, Schmidlin J, et al. (1987) Three new epoxy-spirolactone derivatives: characterization in vivo and in vitro. *J Pharmacol Exp Ther* **240**:650-656.
12. Hu X, Li S, McMahon EG, Lala DS, and Rudolph AE (2005) Molecular mechanisms of mineralocorticoid receptor antagonism by eplerenone. *Mini Rev Med Chem* **5**:709-718.
13. Onate SA, Tsai SY, Tsai MJ, and O'Malley BW (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science (Wash DC)* **270**:1354-1357.
14. Fuse H, Kitagawa H, and Kato S (2000) Characterization of transactivational property and coactivator mediation of rat mineralocorticoid receptor activation function-1 (AF-1). *Mol Endocrinol* **14**:889-899.
15. Pascual-Le Tallec L, Simone F, Viengchareun S, Meduri G, Thirman MJ, and Lombes M (2005) The elongation factor ELL (eleven-nineteen lysine-rich leukemia) is a selective coregulator for steroid receptor functions. *Mol Endocrinol* **19**:1155-1169.
16. Wang Q, Anzick S, Richter WF, Meltzer P, and Simons SS Jr (2004) Modulation of transcriptional sensitivity of mineralocorticoid and estrogen receptors. *J Steroid Biochem Mol Biol* **91**:197-210.
17. Pascual-Le Tallec L, Kirsh O, Lecomte MC, Viengchareun S, Zennaro MC, Dejean A, and Lombes M (2003) Protein inhibitor of activated signal transducer and activator of transcription 1 interacts with the N-terminal domain of mineralocorticoid receptor and represses its transcriptional activity: implication of small ubiquitin-related modifier 1 modification. *Mol Endocrinol* **17**:2529-2542.
18. Pascual-Le Tallec L, Demange C, and Lombes M (2004) Human mineralocorticoid receptor A and B protein forms produced by alternative translation sites display different transcriptional activities. *Eur J Endocrinol* **150**:585-590.

19. Bloem LJ, Guo C, and Pratt JH (1995) Identification of a splice variant of the rat and human mineralocorticoid receptor genes. *J Steroid Biochem Mol Biol* **55**:159–162.
20. Zhou MY, Gomez-Sanchez CE, and Gomez-Sanchez EP (2000) An alternatively spliced rat mineralocorticoid receptor mRNA causing truncation of the steroid binding domain. *Mol Cell Endocrinol* **159**:125–131.
21. Zennaro MC, Souque A, Viengchareun S, Poisson E, and Lombes M (2001) A new human MR splice variant is a ligand-independent transactivator modulating corticosteroid action. *Mol Endocrinol* **15**:1586–1598.
22. Krozowski ZS and Funder JW (1983) Renal mineralocorticoid receptors and hippocampal corticosterone-binding species have identical intrinsic steroid specificity. *Proc Natl Acad Sci USA* **80**:6056–6060.
23. McEwen BS, De Kloet ER, and Rostene W (1986) Adrenal steroid receptors and actions in the nervous system. *Physiol Rev* **66**:1121–1188.
24. Pearce P and Funder JW (1987) High affinity aldosterone binding sites (type I receptors) in rat heart. *Clin Exp Pharmacol Physiol* **14**:859–866.
25. Scott BA, Lawrence B, Nguyen HH, and Meyer WJ 3rd (1987) Aldosterone and dexamethasone binding in human arterial smooth muscle cells. *J Hypertens* **5**:739–744.
26. Arriza JL, Simerly RB, Swanson LW, and Evans RM (1988) The neuronal mineralocorticoid receptor as a mediator of glucocorticoid response. *Neuron* **1**:887–900.
27. Barnett CA and Pritchett EL (1988) Detection of corticosteroid type I binding sites in heart. *Mol Cell Endocrinol* **56**:191–198.
28. Lombes M, Oblin ME, Gasc JM, Baulieu EE, Farman N, and Bonvalet JP (1992) Immunohistochemical and biochemical evidence for a cardiovascular mineralocorticoid receptor. *Circ Res* **71**:503–510.
29. Van Eekelen JA and De Kloet ER (1992) Co-localization of brain corticosteroid receptors in the rat hippocampus. *Prog Histochem Cytochem* **26**:250–258.
30. Kenouch S, Lombes M, Delahaye F, Eugene E, Bonvalet JP, and Farman N (1994) Human skin as target for aldosterone: coexpression of mineralocorticoid receptors and  $11\beta$ -hydroxysteroid dehydrogenase. *J Clin Endocrinol Metab* **79**:1334–1341.
31. Lombes M, Alfaidy N, Eugene E, Lessana A, Farman N, and Bonvalet JP (1995) Prerequisite for cardiac aldosterone action: mineralocorticoid receptor and  $11\beta$ -hydroxysteroid dehydrogenase in the human heart. *Circulation* **92**:175–182.
32. Zennaro MC, Farman N, Bonvalet JP, and Lombes M (1997) Tissue-specific expression of  $\alpha$  and  $\beta$  messenger ribonucleic acid isoforms of the human mineralocorticoid receptor in normal and pathological states. *J Clin Endocrinol Metab* **82**:1345–1352.
33. de Kloet ER, Van Acker SA, Sibug RM, Oitzl MS, Meijer OC, Rahmouni K, and de Jong W (2000) Brain mineralocorticoid receptors and centrally regulated functions. *Kidney Int* **57**:1329–1336.
34. Berger S, Bleich M, Schmid W, Cole TJ, Peters J, Watanabe H, Kriz W, Warth R, Greger R, and Schutz G (1998) Mineralocorticoid receptor knockout mice: pathophysiology of  $\text{Na}^+$  metabolism. *Proc Natl Acad Sci USA* **95**:9424–9429.
35. Skrabal F, Aubock J, Edwards CR, and Braunsteiner H (1978) Subtraction potential difference: in-vivo assay for mineralocorticoid activity. *Lancet* **1**:298–302.
36. Epple HJ, Amasheh S, Mankertz J, Goltz M, Schulzke JD, and Fromm M (2000) Early aldosterone effect in distal colon by transcriptional regulation of ENaC subunits. *Am J Physiol* **278**:G718–G724.
37. Amasheh S, Epple HJ, Mankertz J, Detjen K, Goltz M, Schulzke JD, and Fromm M (2000) Differential regulation of ENaC by aldosterone in rat early and late distal colon. *Ann NY Acad Sci* **915**:92–94.
38. Brennan FE and Fuller PJ (2000) Rapid upregulation of serum and glucocorticoid-regulated kinase (sgk) gene expression by corticosteroids in vivo. *Mol Cell Endocrinol* **166**:129–136.
39. Shigaev A, Asher C, Latter H, Garty H, and Reuveny E (2000) Regulation of sgk by aldosterone and its effects on the epithelial  $\text{Na}^+$  channel. *Am J Physiol* **278**:F613–F619.
40. Bhargava A, Fullerton MJ, Myles K, Purdy TM, Funder JW, Pearce D, and Cole TJ (2001) The serum- and glucocorticoid-induced kinase is a physiological mediator of aldosterone action. *Endocrinology* **142**:1587–1594.
41. Soundararajan R, Zhang TT, Wang J, Vandewalle A, and Pearce D (2005) A novel role for glucocorticoid-induced leucine zipper protein in epithelial sodium channel-mediated sodium transport. *J Biol Chem* **280**:39970–39981.
42. Geller DS, Farhi A, Pinkerton N, Fradley M, Moritz M, Spitzer A, Meinke G, Tsai FT, Sigler PB, and Lifton RP (2000) Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science* **289**:119–123.
43. Geller DS, Rodriguez-Soriano J, Vallo Boado A, Schifter S, Bayer M, Chang SS, Lifton RP (1998) Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. *Nat Genet* **19**:279–281.
44. Geller DS, Zhang J, Zennaro MC, Vallo-Boado A, Rodriguez-Soriano J, Furu L, Haws R, Metzger D, Botelho B, Karaviti L, et al. (2006) Autosomal dominant pseudohypoaldosteronism type 1: mechanisms, evidence for neonatal lethality, and phenotypic expression in adults. *J Am Soc Nephrol* **17**:1429–1436.

TABLE 3  
PR

Receptor nomenclature	NR3C3
Receptor code	4.10.1:PG:3:C3
Other names	PGR, progesterone receptor
Molecular information	Hs: 933aa, P06401, chr. 11q22 <sup>1</sup> Rn: 923aa, Q63449, chr. 8q11 <sup>2</sup> Mm: 923aa, Q00175, chr. 9 A1 <sup>3</sup>
DNA binding	
Structure	Homodimer
HRE core sequence	GGTACANNNTGTTCT (GRE, palindrome)
Partners	HSP90 (physical): cellular localization <sup>4,5</sup> ; HMGB (physical, functional): DNA binding <sup>6,7</sup> Src family kinases (physical): activation of rapid signalling cascades, independent of PR DNA binding <sup>8</sup>
Agonists	Levonorgestrel, medroxyprogesterone,* promegestone (R5020),* dydrogesterone, norethisterone, progesterone (P4) <sup>9</sup>
Antagonists	Asoprisnil, mifepristone (RU486),* RTI 3021-012, RTI 3021-022, onapristone (ZK98299)
Coactivator	NCOA1, NCOA3, CREBBP, SRA1, JDP2 <sup>10-20</sup>
Corepressor	NCOR2 <sup>21-24</sup>
Biologically important isoform	PRA {Hs, Mm, Rn}: N-terminally truncated isoform that is a weak transcriptional activator of specific target genes in a cell type-dependent manner and a strong repressor of transactivation by PRB and other steroid receptors <sup>25,26</sup> ; PRB{Hs}: full-length protein that strongly activates target genes <sup>27</sup>
Tissue distribution	Mammary gland, uterus, brain, muscle, testis, ovary (Hs, Mm, Rn) [Northern blot, in situ hybridization, Western blot, immunohistology] <sup>28,29</sup>
Functional assay	Inhibition of proliferation in endometrial cells caused by treatment of ovariectomized (estrogen-treated) mice with progesterone{Mm} <sup>30,31</sup> ; proliferation in PR-positive breast cancer cells and normal breast epithelial cells{Hs} <sup>32,33</sup> ; mammary gland ductal tree branching and lobuloalveolar development in ovariectomized (estrogen-treated) mice treated with progesterone{Mm} <sup>34,35</sup>
Main target genes	Activated: FSH $\beta$ , <sup>36</sup> multidrug resistance 1B{Mm}, <sup>37</sup> Stat5A{Hs}, <sup>38</sup> 11 $\beta$ -hydroxysteroid dehydrogenase{Hs}, <sup>38</sup> Indian hedgehog{Mm} <sup>39</sup>
Mutant phenotype	Disruption of both PRA and B isoforms results in impaired sexual behavior, anovulation, uterine dysfunction, and reduced ductal branching and lobuloalveolar development in the mammary gland {Mm} [knockout] <sup>40</sup> ; targeted overexpression of PRA in the mammary gland results in reduced induction of apoptosis {Mm} [overexpression] <sup>41</sup>
Human disease	Pseudocorpus luteum insufficiency: due to decreased PR expression <sup>42</sup> ; breast cancer: higher PRA/PRB ratio correlates with increased tumor grade <sup>43</sup> ; endometriosis: due to reduced expression of PRB (not PRA) in diseased tissue <sup>44,45</sup> ; endometrial cancer: increased risk caused by polymorphisms in the PR promoter favoring expression of PRB <sup>46,47</sup>

aa, amino acids; chr., chromosome; HRE, hormone response element; HMGB, chromosomal high mobility group B; Q-PCR, quantitative polymerase chain reaction; GRE, glucocorticoid response element; CREBBP, cAMP response element binding protein binding protein.

\* Radioligand.

- Mattei MG, Krust A, Stropp U, Mattei JF, and Chambon P (1988) Assignment of the human progesterone receptor to the q22 band of chromosome 11. *Hum Genet* **78**:96–97.
- Johansson A, Helou K, and Levan G (1998) Cytogenetic localization of cancer-related genes in the rat and comparative mapping studies in human and mouse. *Cytogenet Cell Genet* **81**:217–221.
- Naylor SL, Helen-Davis D, Hughes MR, O'Malley BW, and Lalley PA (1989) The progesterone receptor gene is on mouse chromosome 9. *Cytogenet Cell Genet* **51**:1051.
- Elbi C, Walker DA, Romero G, Sullivan WP, Toft DO, Hager GL, DeFranco DB (2004) Molecular chaperones function as steroid receptor nuclear mobility factors. *Proc Natl Acad Sci USA* **101**:2876–2881.
- Sullivan WP and Toft DO (1993) Mutational analysis of hsp90 binding to the progesterone receptor. *J Biol Chem* **268**:20373–20379.
- Boonyaratanakornkit V, Scott MP, Ribon V, Sherman L, Anderson SM, Maller JL, Miller WT, and Edwards DP (2001) Progesterone receptor contains a proline-rich motif that directly interacts with SH3 domains and activates c-Src family tyrosine kinases. *Mol Cell* **8**:269–280.
- Onate SA, Prendergast P, Wagner JP, Nissen M, Reeves R, Pettijohn DE, and Edwards DP (1994) The DNA-binding protein HMG-1 enhances progesterone receptor binding to its target DNA sequences. *Mol Cell Biol* **14**:3376–3391.
- Boonyaratanakornkit V, Scott MP, Ribon V, Sherman L, Anderson SM, Maller JL, Miller WT, and Edwards DP (2001) Progesterone receptor contains a proline-rich motif that directly interacts with SH3 domains and activates c-Src family tyrosine kinases. *Mol Cell* **8**:269–280.
- Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, and Thijssen JH (2003) Classification and pharmacology of progestins. *Maturitas* **46**:S7–S16.
- Anzick SL, Kononen J, Walker RL, Azorsa DO, Tanner MM, Guan XY, Sauter G, Kallioniemi OP, Trent JM, and Meltzer PS (1997) AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. *Science (Wash DC)* **277**:965–968.
- Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, and Evans RM (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell* **90**:556–580.
- Lanz RB, McKenna NJ, Onate SA, Albrecht U, Wong J, Tsai SY, Tsai MJ, and O'Malley BW (1999) A steroid receptor coactivator, SRA, functions as an RNA and is present in an SRC-1 complex. *Cell* **97**:17–27.
- Li X, Wong J, Tsai SY, Tsai MJ, and O'Malley BW (2003) Progesterone and glucocorticoid receptors recruit distinct coactivator complexes and promote distinct patterns of local chromatin modification. *Mol Cell Biol* **23**:3763–3773.
- Liu Z, Wong J, Tsai SY, Tsai MJ, and O'Malley BW (1999) Steroid receptor coactivator-1 (SRC-1) enhances ligand-dependent and receptor-dependent cell-free transcription of chromatin. *Proc Natl Acad Sci USA* **96**:9485–9490.
- Sheppard HM, Harries JC, Hussain S, Bevan C, and Heery DM (2001) Analysis of the steroid receptor coactivator 1 (SRC1)-CREB binding protein interaction interface and its importance for the function of SRC1. *Mol Cell Biol* **21**:39.
- Shi Y, Downes M, Xie W, Kao HY, Ordentlich P, Tsai CC, Hon M, and Evans RM (2001) Sharp, an inducible cofactor that integrates nuclear receptor repression and activation. *Genes Dev* **15**:1140–1151.
- Shiozawa T, Shih HC, Miyamoto T, Feng YZ, Uchikawa J, Itoh K, and Konishi I (2003) Cyclic changes in the expression of steroid receptor coactivators and corepressors in the normal human endometrium. *J Clin Endocrinol Metab* **88**:871–878.
- Smith CL, Onate SA, Tsai MJ, and O'Malley BW (1996) CREB binding protein acts synergistically with steroid receptor coactivator-1 to enhance steroid receptor-dependent transcription. *Proc Natl Acad Sci USA* **93**:8884–8888.

19. Spencer TE, Jenster G, Burcin MM, Allis CD, Zhou J, Mizzen CA, McKenna NJ, Onate SA, Tsai SY, Tsai MJ, et al. (1997) Steroid receptor coactivator-1 is a histone acetyltransferase. *Nature (Lond)* **389**:194–198.
20. Wardell SE, Boonyaratankornkit V, Adelman JS, Aronheim A, and Edwards DP (2002) Jun dimerization protein 2 functions as a progesterone receptor N-terminal domain coactivator. *Mol Cell Biol* **22**:5451–5466.
21. Giangrande PH, Kimbrel EA, Edwards DP, and McDonnell DP (2000) The opposing transcriptional activities of the two isoforms of the human progesterone receptor are due to differential cofactor binding. *Mol Cell Biol* **20**:3102–3115.
22. Liu Z, Auboeuf D, Wong J, Chen JD, Tsai SY, Tsai MJ, and O'Malley BW (2002) Coactivator/corepressor ratios modulate PR-mediated transcription by the selective receptor modulator RU486. *Proc Natl Acad Sci USA* **99**:7940–7944.
23. Nagy L, Kao HY, Chakravarti D, Lin RJ, Hassig CA, Ayer DE, Schreiber SL, and Evans RM (1997) Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase. *Cell* **89**:373–380.
24. Wagner BL, Norris JD, Knotts TA, Weigel NL, and McDonnell DP (1998) The nuclear corepressors NCoR and SMRT are key regulators of both ligand- and 8-bromo-cyclic AMP-dependent transcriptional activity of the human progesterone receptors. *Mol Cell Biol* **18**:1369–1378.
25. Giangrande PH, Pollio G, and McDonnell DP (1997) Mapping and characterization of the functional domains responsible for the differential activity of the A and B isoforms of the human progesterone receptor. *J Biol Chem* **272**:32889–32900.
26. Vegeto E, Shahbaz MM, Wen DX, Goldman ME, O'Malley BW, and McDonnell DP (1993) Human progesterone receptor A form is a cell- and promoter-specific repressor of human progesterone receptor B function. *Mol Endocrinol* **7**:1244–1255.
27. Kastner P, Krust A, Turcotte B, Stropp U, Tora L, Gronemeyer H, and Chambon P (1990) Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. *EMBO (Eur Mol Biol Organ) J* **9**:1603–1614.
28. Mangal RK, Wiehle RD, Poindexter ANR, and Weigel NL (1997) Differential expression of uterine progesterone receptor forms A and B during the menstrual cycle. *J Steroid Biochem Mol Biol* **63**:195–2002.
29. Robker RL, Russell DL, Espey LL, Lydon JP, O'Malley BW, and Richards JS (2000) Progesterone-regulated genes in the ovulation process: ADAMTS-1 and cathepsin L proteases. *Proc Natl Acad Sci USA* **97**:4689–4694.
30. Finn CA and Pope M (1984) Vascular and cellular changes in the decidualized endometrium of the ovariectomized mouse following cessation of hormone treatment: a possible model for menstruation. *J Endocrinol* **100**:295–300.
31. Parandoosh Z, Crombie DL, Tetzke TA, Hayes JS, Heap RB, and Wang MW (1995) Progesterone and oestrogen receptors in the decidualized mouse uterus and effects of different types of anti-progesterone treatment. *J Reprod Fertil* **105**:215–220.
32. Kramer EA, Seeger H, Kramer B, Wallwiener D, and Mueck AO (2005) The effects of progesterone, medroxyprogesterone acetate, and norethisterone on growth factor- and estradiol-treated human cancerous and noncancerous breast cells. *Menopause* **12**:468–474.
33. Saitoh M, Ohmichi M, Takahashi K, Kawagoe J, Ohta T, Doshida M, Takahashi T, Igarashi H, Mori-Abe A, Du B, et al. (2005) Medroxyprogesterone acetate induces cell proliferation through upregulation of cyclin D1 expression via P13K/Akt/NF kappa B cascade in human breast cancer cells. *Endocrinology* **146**:4917–4925.
34. Aupperlee MD, Smith KT, Kariagina A, and Haslam SZ (2005) Progesterone receptor isoforms A and B: temporal and spatial differences in expression during murine mammary gland development. *Endocrinology* **146**:3577–3588.
35. Ismail PM, Amato P, Soyak SM, DeMayo FJ, Conneely OM, O'Malley BW, and Lydon JP (2003) Progesterone involvement in breast development and tumorigenesis—as revealed by progesterone receptor 'knockout' and 'knockin' mouse models. *Steroids* **68**:779–787.
36. Webster JC, Pedersen NR, Edwards DP, Beck CA, and Miller WL (1995) The 5'-flanking region of the ovine follicle-stimulating hormone- $\beta$  gene contain six progesterone response elements: three proximal elements are sufficient to increase transcription in the presence of progesterone. *Endocrinology* **136**:1049–1058.
37. Mallick S and Horwitz SB (1997) Transcriptional regulation of the murine multidrug resistance gene *mdr1b* by progesterone occurs via an indirect mechanism. *DNA Cell Biol* **16**:807–818.
38. Richer JK, Jacobsen BM, Manning NG, Abel MG, Wolf DM, and Horwitz KB (2002) Differential gene regulation by the two progesterone receptor isoforms in human breast cancer cells. *J Biol Chem* **277**:5209–5218.
39. Takamoto N, Zhao B, Tsai SY, and DeMayo FJ (2002) Identification of Indian hedgehog as a progesterone-responsive gene in the murine uterus. *Mol Endocrinol* **16**:2338–2348.
40. Lydon JP, DeMayo FJ, Funk CR, Mani SK, Hughes AR, CA Montgomery J, Shyamala G, Conneely OM, and O'Malley BW (1995) Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. *Genes Dev* **9**:2266–2278.
41. Shyamala G, Yang X, Silberstein G, Barcellos-Hoff MH, and Dale E (1998) Transgenic mice carrying an imbalance in the native ratio of A to B forms of progesterone receptor exhibit developmental abnormalities in mammary glands. *Proc Natl Acad Sci USA* **95**:696–701.
42. Keller DW, Wiest WG, Askin FB, Johnson LW, and Strickler RC (1979) Pseudocorpus luteum insufficiency: a local defect of progesterone action on endometrial stroma. *J Clin Endocrinol Metab* **48**:127–132.
43. Bamberger AM, Milde-Langosch K, Schulte HM, and Loning T (2000) Progesterone receptor isoforms, PR-B and PR-A, in breast cancer: correlations with clinicopathologic tumor parameters and expression of AP-1 factors. *Horm Res* **54**:32–37.
44. Attia GR, Zeitoun K, Edwards D, Johns A, Carr BR, and Bulun SE (2000) Progesterone receptor isoform A but not B is expressed in endometriosis. *J Clin Endocrinol Metab* **85**:2897–2902.
45. Chwalisz K, DeManno D, Garg R, Larsen L, Mattia-Goldberg C, and Stickler T (2004) Therapeutic potential for the selective progesterone receptor modulator asoprisnil in the treatment of leiomyomata. *Semin Reprod Med* **22**:113–119.
46. De Vivo I, Huggins GS, Hankinson SE, Lescault PJ, Boezen M, Colditz GA, and Hunter DJ (2002) A functional polymorphism in the promoter of the progesterone receptor gene associated with endometrial cancer risk. *Proc Natl Acad Sci USA* **99**:12263–12268.
47. Terry KL, De Vivo I, Titus-Ernstoff L, Sluss PM, and Cramer DW (2005) Genetic variation in the progesterone receptor gene and ovarian cancer risk. *Am J Epidemiol* **161**:442–451.

TABLE 4  
AR

Receptor nomenclature	NR2B1
Receptor code	4.10.1:AG:3:C4
Other names	AIS, DHTR, dihydrotestosterone receptor, HUMARA, KD, NR3C4, SBMA, SMAX1, TFM
Molecular information	Hs: 919aa, P10275, chr. Xq11 <sup>1,2</sup> Rn: 902aa, P15207, chr. Xq22 <sup>3</sup> Mm: 899aa, P19091, chr. X C3 <sup>4-6</sup>
DNA binding	
Structure	Homodimer
HRE core sequence	GGTACANNNTGTTCT (GRE, palindrome)
Partners	HSP90 (physical): cellular localization, specify protein stability <sup>7,8</sup> ; HMGB (physical, functional): DNA binding <sup>9,10</sup>
Agonists	Mibolerone (1.65 nM),* DHT (2.23 nM), androstenedione (2.75 nM), methyltrienolone (3.07 nM),* testosterone (15.9 nM)* [IC <sub>50</sub> ] <sup>2</sup>
Fluoxymesterone	
Antagonists	Hydroxyflutamide, bicalutamide, nilutamide, mifepristone, cyproterone acetate
Coactivators	RNF14, NCOA2, NCOA4, Fhl2, TGFB1I1, RAN <sup>11-24</sup>
Biologically important isoforms	AR-A {Hs}:187aa truncated from the N terminus <sup>25-28</sup> ; AR-B {Hs}: 110 kDa <sup>25-28</sup>
Tissue distribution	Bone marrow, mammary gland, muscle, prostate, stem cells, testes, preputial gland, scrotal skin, vagina {Rn} [Western blot] <sup>29</sup>
Functional assay	Treatment of castrated rats with AR ligands possessing anabolic activity results in increased skeletal muscle mass {Rn} <sup>30</sup> ; androgen treatment causes increased expression of sex hormone-binding globulin in the hepatocarcinoma cell line HepG2 {Hs} <sup>31</sup> ; treatment of castrated rats with AR ligands possessing anabolic activity results in increased weight of prostate and seminal vesicles {Rn} <sup>30</sup>
Main target genes	Activated: PSA (Hs, Rn, Mm), <sup>32,33</sup> probasin {Rn}, <sup>34</sup> Slp {Mm}, <sup>35</sup> prostatein C3 {Rn}, <sup>36</sup> SC {Hs} <sup>37,38</sup>
Mutant phenotype	Male mice lacking AR <sup>-/-</sup> exhibit insulin resistance and impaired glucose tolerance {Mm} [knockout] <sup>39-41</sup> ; male mice lacking AR in Sertoli cells exhibit infertility with defective spermatogenesis and hypotestosteronemia {Mm} [knockout] <sup>42</sup>
Human disease	Prostate cancer: mutations of AR affecting ligand binding as well as gene amplification of AR have been described <sup>43</sup> ; androgen insensitivity syndrome: mutations of AR affecting ligand binding, DNA binding or nuclear localization <sup>44,45</sup> ; Kennedy's disease (poly-Q): spinobulbar muscular atrophy is an X-linked form of motor neuron disease characterized by progressive atrophy of the muscles, dysphagia, dysarthria, and mild androgen insensitivity caused by CAG repeat expansion in the AR gene <sup>46-48</sup> ; Klinefelter's syndrome (47, XXY, hypogonadism): characterized by undeveloped testes and sterility, skewed inactivation of the X-chromosome seems to contribute to reduced AR expression <sup>49,50</sup>

aa, amino acids; chr., chromosome; HRE, hormone response element; DHT, dihydrotestosterone; GRE, glucocorticoid response element.

\* Radioligand.

- Brown CJ, Goss SJ, Lubahn DB, Joseph DR, Wilson EM, French FS, and Willard HF (1989) Androgen receptor locus on the human X chromosome: regional localization to Xq11-12 and description of a DNA polymorphism. *Am J Hum Genet* **44**:264-269.
- Fang H, Tong W, Branham WS, Moland CL, Dial SL, Hong H, Xie Q, Perkins R, Owens W, and Sheehan DM (2003) Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. *Chem Res Toxicol* **16**:1338-1358.
- Tan JA, Joseph DR, Quarumby VE, Lubahn DB, Sar M, French FS, and Wilson EM (1988) The rat androgen receptor: primary structure, autoregulation of its messenger ribonucleic acid, and immunocytochemical localization of the receptor protein. *Mol Endocrinol* **2**:1276-1285.
- Eicher EM, Nesbitt MN, and Francke U (1972) Cytological identification of the chromosomes involved in Searle's translocation and the location of the centromere in the X chromosome of the mouse. *Genetics* **71**:643-648.
- Francke, U. and Taggart, R.T. (1980) Comparative gene mapping: order of loci on the X chromosome is different in mice and humans. *Proc Natl Acad Sci USA* **77**:3595-3599.
- Lyon MF and Hawkes SG (1970) X-linked gene for testicular feminization in the mouse. *Nature (Lond)* **227**:1217-1219.
- Georget V, Terouanne B, Nicolas JC, and Sultan C (2002) Mechanism of antiandrogen action: key role of hsp90 in conformational change and transcriptional activity of the androgen receptor. *Biochemistry* **41**:11824-11831.
- Marivoet S, Dijk PV, Verhoeven G, and Heyns W (1992) Interaction of the 90-kDa heat shock protein with native and in vitro translated androgen receptor and receptor fragments. *Mol Cell Endocrinol* **88**:165-174.
- Boonyaratankornkit V, Melvin V, Prendergast P, Altmann M, Ronfani L, Bianchi ME, Taraseviciene L, Nordeen SK, Allegretto EA, and Edwards DP (1998) High-mobility group chromatin proteins 1 and 2 functionally interact with steroid hormone receptors to enhance their DNA binding in vitro and transcriptional activity in mammalian cells. *Mol Cell Biol* **18**:4471-4487.
- Verrijdt G, Haelens A, Schoenmakers E, Rombauts W, and Claessens F (2002) Comparative analysis of the influence of the high-mobility group box 1 protein on DNA binding and transcriptional activation by the androgen, glucocorticoid, progesterone and mineralocorticoid receptors. *Biochem J* **361**:97-103.
- Chan KK, Tsui SK, Ngai SM, Lee SM, Kotaka M, Waye MM, Lee CY, and Fung KP (2000) Protein-protein interaction of FHL2, a LIM domain protein preferentially expressed in human heart, with hCDC47. *J Cell Biochem* **76**:499-508.
- Fujimoto N, Yeh S, Kang HY, Inui S, Chang HC, Mizokami A, and Chang C (1999) Cloning and characterization of androgen receptor coactivator, ARA55, in human prostate. *J Biol Chem* **274**:8316-8321.
- Geserick C, Meyer HA, Barbulescu K, and Haendler B (2003) Differential modulation of androgen receptor action by deoxyribonucleic acid response elements. *Mol Endocrinol* **17**:1738-1750.
- Hsiao PW, Lin DL, Nakao R, and Chang C (1999) The linkage of Kennedy's neuron disease to ARA24, the first identified androgen receptor polyglutamine region-associated coactivator. *J Biol Chem* **274**:20229-20234.
- Hu YC, Yeh S, Yeh SD, Sampson ER, Huang J, Li P, Hsu CL, Ting HJ, Lin HK, Wang L, et al. (2004) Functional domain and motif analyses of androgen receptor coregulator ARA70 and its differential expression in prostate cancer. *J Biol Chem* **279**:33438-33446.
- Itō K, Adachi S, Iwakami R, Yasuda H, Muto Y, Seki N, and Okano Y (2001) N-terminally extended human ubiquitin-conjugating enzymes (E2s) mediate the ubiquitination of RING-finger proteins, ARA54 and RNF8. *Eur J Biochem* **268**:2725-2732.
- Kang HY, Yeh S, Fujimoto N, and Chang C (1999) Cloning and characterization of human prostate coactivator ARA54, a novel protein that associates with the androgen receptor. *J Biol Chem* **274**:8570-8576.

18. Kang Z, Pirskanen A, Janne OA, and Palvimo JJ (2002) Involvement of proteasome in the dynamic assembly of the androgen receptor transcription complex. *J Biol Chem* **277**:48366–48371.
19. Mestayer C, Blanchere M, Jaubert F, Dufour B, and Mowszowicz I (2003) Expression of androgen receptor coactivators in normal and cancer prostate tissues and cultured cell lines. *Prostate* **56**:192–200.
20. Miyamoto H, Rahman M, Takatera H, Kang HY, Yeh S, Chang HC, Nishimura K, Fujimoto N, and Chang C (2002) A dominant-negative mutant of androgen receptor coregulator ARA54 inhibits androgen receptor-mediated prostate cancer growth. *J Biol Chem* **277**:4609–4617.
21. Miyoshi Y, Ishiguro H, Uemura H, Fujinami K, Miyamoto H, Miyoshi Y, Kitamura H, and Kubota Y (2003) Expression of AR associated protein 55 (ARA55) and androgen receptor in prostate cancer. *Prostate* **56**:280–286.
22. Muller JM, Isele U, Metzger E, Rempel A, Moser M, Pscherer A, Breyer T, Holubarsch C, Buettner R, and Schule R (2000) FHL2, a novel tissue-specific coactivator of the androgen receptor. *EMBO (Eur Mol Biol Organ) J* **19**:359–369.
23. Ye X, Han SJ, Tsai SY, DeMayo FJ, Xu J, Tsai MJ, and O'Malley BW (2005) Roles of steroid receptor coactivator (SRC)-1 and transcriptional intermediary factor (TIF) 2 in androgen receptor activity in mice. *Proc Natl Acad Sci USA* **102**:9487–9492.
24. Yeh S, Sampson ER, Lee DK, Kim E, Hsu CL, Chen YL, Chang HC, Altuwajri S, Huang KE, and Chang C (2000) Functional analysis of androgen receptor N-terminal and ligand binding domain interacting coregulators in prostate cancer. *J Formos Med Assoc* **99**:885–894.
25. Gao T and McPhaul MJ (1998) Functional activities of the A and B forms of the human androgen receptor in response to androgen receptor agonists and antagonists. *Mol Endocrinol* **12**:654–663.
26. Liegibel UM, Sommer U, Boercoek I, Hilscher U, Bierhaus A, Schweikert HU, Nawroth P, and Kasperk C (2003) Androgen receptor isoforms AR-A and AR-B display functional differences in cultured human bone cells and genital skin fibroblasts. *Steroids* **68**:1179–1187.
27. Wilson CM and McPhaul MJ (1994) A and B isoforms of the androgen receptor are present in human genital skin fibroblasts. *Proc Natl Acad Sci USA* **91**:1234–1238.
28. Wilson CM and McPhaul MJ (1996) A and B isoforms of the androgen receptor are expressed in a variety of human tissues. *Mol Cell Endocrinol* **120**:51–57.
29. Bentvelsen FM, McPhaul MJ, Wilson CM, Wilson JD, and George FW (1996) Regulation of immunoreactive androgen receptor in the adrenal gland of the adult rat. *Endocrinology* **137**:2659–2663.
30. Yin D, Gao W, Kearbey JD, Xu H, Chung K, Marhefka CA, Veverka KA, Miller DD, and Dalton JT (2003) Pharmacodynamics of selective androgen receptor modulators. *J Pharmacol Exp Ther* **304**:1334–1340.
31. Lee IR, Dawson SA, Wetherall JD, and Hahnel R (1987) Sex hormone-binding globulin secretion by human hepatocarcinoma cells is increased by both estrogens and androgens. *J Clin Endocrinol Metab* **64**:825–831.
32. Cleutjens KB, Eekelen CCV, Korput HAVD, Brinkmann AO, and Trapman J (1996) Two androgen response regions cooperate in steroid hormone regulated activity of the prostate-specific antigen promoter. *J Biol Chem* **271**:6379–6388.
33. Zhang S, Murtha PE, and Young CY (1997) Defining a functional androgen responsive element in the 5' far upstream flanking region of the prostate-specific antigen gene. *Biochem Biophys Res Commun* **231**:784–788.
34. Rennie PS, Bruchoovsky N, Leco KJ, Sheppard PC, McQueen SA, Cheng H, Snoek R, Hamel A, Bock ME, and MacDonald BS (1993) Characterization of two cis-acting DNA elements involved in the androgen regulation of the probasin gene. *Mol Endocrinol* **7**:23–36.
35. Scheller A, Scheinman RI, Thompson E, Scarlett, CO, and Robins DM (1996) Contextual dependence of steroid receptor function on an androgen-responsive enhancer. *Mol Cell Endocrinol* **121**:75–86.
36. Tan JA, Marschke KB, Ho KC, Perry ST, Wilson EM, and French FS (1992) Response elements of the androgen-regulated C3 gene. *J Biol Chem* **267**:4456–4466.
37. Haelens A, Verrijdt G, Callewaert L, Peeters B, Rombauts W, and Claessens F (2001) Androgen-receptor-specific DNA binding to an element in the first exon of the human secretory component gene. *Biochem J* **353**:611–620.
38. Verrijdt G, Schoenmakers E, Alen P, Haelens A, Peeters B, Rombauts W, and Claessens F (1999) Androgen specificity of a response unit upstream of the human secretory component gene is mediated by differential receptor binding to an essential androgen response element. *Mol Endocrinol* **13**:558–1570.
39. Fan W, Yanase T, Nomura M, Okabe T, Goto K, Sato T, Kawano H, Nato S, and Nawata H (2005) Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipolytic activity but show normal insulin sensitivity with high adiponectin secretion. *Diabetes* **54**:1000–1008.
40. Lin HY, Xu Q, Yeh S, Wang RS, Sparks JD, and Chang C (2005) Insulin and leptin resistance with hyperleptinemia in mice lacking androgen receptor. *Diabetes* **54**:1717–1725.
41. Sato T, Matsumoto T, Yamada T, Watanabe T, Kawano H, and Kato S (2003) Late onset of obesity in male androgen receptor -deficient (AR KO) mice. *Biochem Biophys Res Commun* **300**:167–171.
42. Chang C, Chen YT, Yeh SD, Xu Q, Wang RS, Guillou F, Lardy H, and Yeh S (2004) Infertility with defective spermatogenesis and hypotestosteronemia in male mice lacking the androgen receptor in Sertoli cells. *Proc Natl Acad Sci USA* **101**:6876–6881.
43. Linja MJ and Visakorpi T (2004) Alterations of androgen receptor in prostate cancer. *J Steroid Biochem Mol Biol* **92**:255–264.
44. Choeng CS, Sturm MJ, Strophair JA, McCulloch RK, and Hurley DM. (1997) Reduced expression and normal nucleotide sequence of androgen receptor gene coding and promoter regions in a family with partial androgen insensitivity syndrome. *Clin Endocrinol (Oxf)* **46**:281–288.
45. Kawate H, Wu Y, Ohnaka K, Tao RH, Nakamura KI, Okabe T, Yanase T, Nawata H, and Takayanagi R (2005) Impaired nuclear translocation, nuclear matrix targeting and intranuclear mobility of mutant androgen receptors carrying amino acid substitutions in the DNA-binding domain derived from androgen insensitivity syndrome patients. *J Clin Endocrinol Metab* **90**:6162–6169.
46. MacLean HE, Choi WT, Rekaris G, Warne GL, and Zajac JD (1995) Abnormal androgen receptor binding affinity in subjects with Kennedy's disease (spinal and bulbar muscular atrophy). *J Clin Endocrinol Metab* **80**:508–516.
47. Neuschmid-Kaspar F, Gast A, Peterziel H, Schneikert J, Muigg A, Ransmayr G, Klocker H, Bartsch G, and Cato AC (1996) CAG-repeat expansion in androgen receptor in Kennedy's disease is not a loss of function mutation. *Mol Cell Endocrinol* **117**:149–156.
48. Sulek A, Hoffman-Zacharska D, Krysa W, Szirkowicz W, Fidzianska E, and Zaremba J (2005) CAG repeat polymorphism in the androgen receptor (AR) gene of SBMA patients and a control group. *J Appl Genet* **46**:237–239.
49. Iitsuka Y, Bock A, Nguyen DD, Samango-Sprouse CA, Simpson JL, and Bischoff FZ (2001) Evidence of skewed X-chromosome inactivation in 47,XXY and 48,XXYY Klinefelter patients. *Am J Med Genet* **98**:25–31.
50. Kotula-Balak M, Bablok L, Fracki S, Jankowska A, and Bilinska B (2004) Immunoprecipitation of androgen receptors and aromatase in testes of patient with Klinefelter's syndrome. *Folia Histochem Cytobiol* **42**:215–220.