**Nuclear Receptor Resource**
Research Article
***The Androgen Receptor***
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# The Androgen Receptor

## 1 Overview

The androgenic hormones testosterone and dihydrotestosterone, which are the ligands of the androgen receptor (AR), are involved in male sexual development, prostate growth, musculoskeletal development, and maintenance of bone mass. The AR, like other nuclear receptors, exerts its effects predominantly as a ligand-activated transcription factor with small molecules acting as agonists, antagonists and selective receptor modulators (SRMs). Synthetic AR ligands with inhibitory activity have been developed to treat benign prostatic hyperplasia and prostate cancer. The current drug development priority is selective AR modulators, to harness receptor antagonism for the prostate disorders and receptor agonism for indications such as osteoporosis and frailty. The androgen receptor is also a target for endocrine disrupting environmental chemicals. Ubiquitous pollutants such as bisphenol A (BPA) and organochlorine pesticides are AR antagonists and as such may pose a human health risk. Due to these two contradictory avenues of research, the AR is a widely studied nuclear receptor in both pharmaceutical and governmental laboratories.

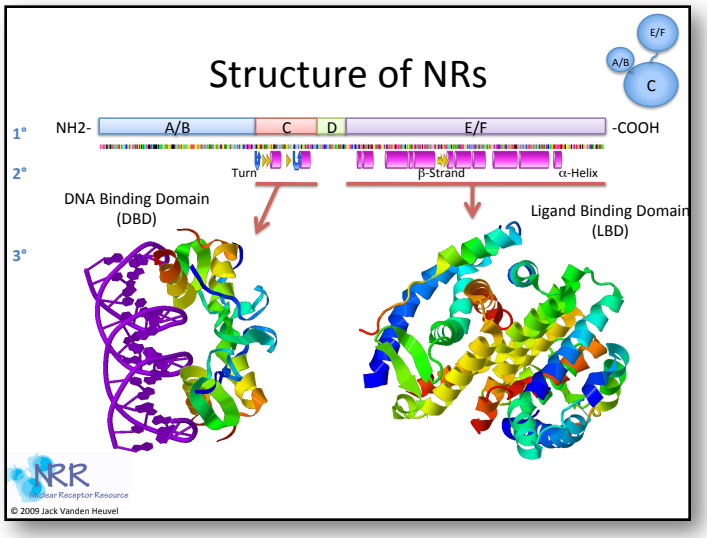


*Figure 1. Basic Structure of the androgen receptor*

## 2. Basic Mechanism of Action

Similar to other Nuclear Receptors (NRs) the AR has distinct functional domains that include the C-terminal ligand binding domain (LBD), a DNA-binding domain (DBD), and an N-terminal, hypervariable domain (NTD) (see Figure 1). The AR DBD has been crystallized, which would allow for rational drug design, but the high degree of homology of this domain with other steroid hormone receptors may predict poor specificity and toxic side effects (Bennett et al., 2010). The transcriptional activity of most steroid hormone receptors is predominantly through the activation function (AF)-2 region in the LBD, the exception being the AR in which it is the AF-1 region in the NTD that contributes most of the transcriptional activity. AR LBD functions independently of the NTD and can still bind ligand even if the AF-1 region is deleted or mutated; however, no transcriptional activity can be achieved without the AF-1 region in the NTD.

The mechanism of action of AR, as a representative member of the "class I" NR (Chen, 2008) is that, in the absence of ligand, the protein is located in the cytosol. Hormone or agonist binding to the AR triggers dissociation of heat shock proteins (HSP), homodimerization, and translocation to the nucleus, where the NR binds to a specific sequence of DNA known as an androgen response element (ARE). The AR/DNA complex in turn recruits other proteins that are responsible for transcription of downstream DNA into mRNA, which is eventually translated into protein, which results in a change in cell function.

Due to the importance of the genes it regulates, in particular in the prostate (see Figure 2), AR remains one of the most studied members of the steroid hormone receptor family of genes. Normal prostate growth and development as well as prostate carcinogenesis are dependent on AR expression and function (Koochekpour, 2010). As an oversimplified statement, the prostate gland at any state of normal or neoplastic development

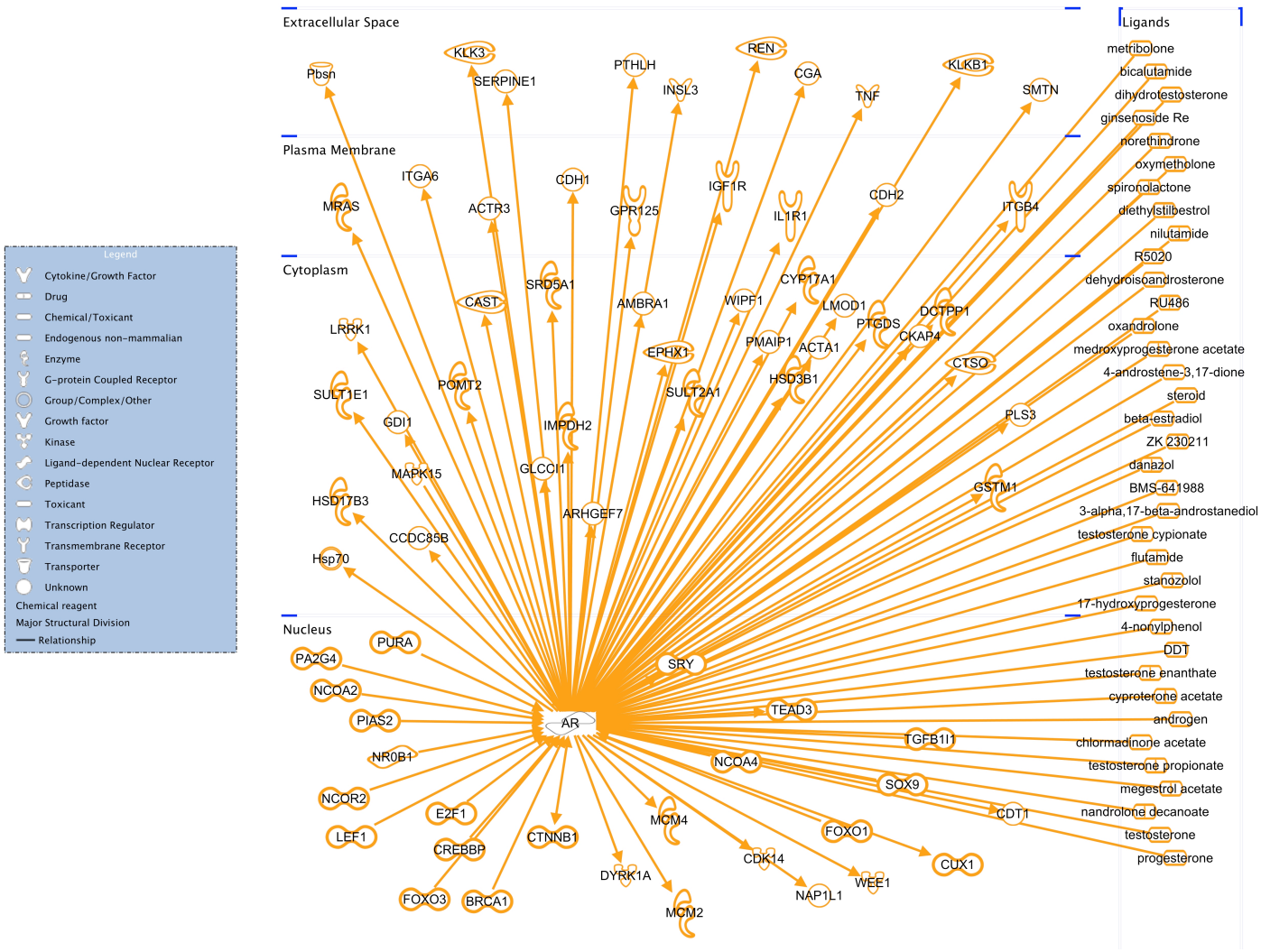


*Figure 2. Regulation of gene expression by AR. Shown are ligands that interact with the AR, as well as the genes that are affected upon agonist or antagonist interaction. Figure was generated by Ingenuity Pathway Analysis (Ingenuity Systems, Inc. Redwood City, CA)*

requires AR activity to sustain grwoth. Alterations in AR structure, expression and signaling could have a determining role in prostate cancer progression. These alterations could be secondary to somatic or germline mutations, presence or absence of nonandrogenic ligands, cytoplasmic signaling crosstalk with other kinases or cross-modulation by other nuclear transcription factors. For a review of these pathways, the reader is directed to other review articles (Gao, 2010; Koochekpour, 2010; Sadar, 2011; Bennett et al., 2010; Lamont and Tindall, 2011).

## 3. Androgen Receptor as a therapeutic target

Androgens are associated with accelerated prostate cancer growth, as well as stimulating the sebaceous glands and promoting hair growth and acne; accordingly, synthetic AR ligands with inhibitory activity have been developed to treat benign prostatic hyperplasia, prostate cancer, and hirsutism. Currently, all conventional therapy has

concentrated on androgen-dependent activation of the AR through its C-terminal LBD (Sadar, 2011). These therapies include reduction of androgen that binds to the LBD by chemical antagonists or inhibitors of production of androgen from cholesterol precursors by prostate cancer cells. There is renewed interest in inhibitors of androgen synthesis. These inhibitors include ketoconazole and, currently in clinical trials, the 17,20-lyase/ CYP17 inhibitor abiraterone, TOK-001, and TAK-700. In addition to inhibiting 17,20-lyase activity to reduce synthesis of androgen, ketoconazole and TOK-001 (VN/124–1) also have antiandrogen activity. Antiandrogens competitively bind AR LBD. Antiandrogens used for the clinical management of prostate cancer include bicalutamide, flutamide, nilutamide, cyproterone acetate, and investigational compounds MDV3100 and ARN-509.

## 4. Environmental Androgen Receptor Modulators

Male sexual differentiation is driven by androgens produced by the fetal testes and is entirely androgen-dependent. Consequently, it is expected that endocrine-disrupting chemicals (EDCs) that interfere with androgen action will have a greater impact on male developmental programming and reproductive tract maturation. The link between environmental contaminants and endocrine activity, including male fertility issues, has been appreciated since the early 1960s (Luccio-Camelo and Prins, 2011). Much like that described for therapeutic drugs, small molecule androgen receptor-mediated disruptors can be classified into agonists and antagonists. An agonist binds to androgen receptor and triggers a response mimicking the action of a naturally occurring androgen while an antagonist acts opposite to an agonist and blocks androgen receptor transactivation. Thus far, there are limited studies on screening of androgen receptor bind- ing activity for a large number of chemicals. However, as reviewed elsewhere (Luccio-Camelo and Prins, 2011), there are many important environmental AR modulators. Agonists include tetrabromoethyl-cyclohexanes (TBECHs) which is brominated flame retardant used in a variety of products. Antagonists are more prevalent and include widely dispersed pesticides and industrial chemicals such as dichlorodiphenyltrichloroethanes (DDTs), bisphenol A (BPA), Vinclozolin, Linuron, Aldrin and Butylbenzylphthalate. While further research at all levels is required to provide detailed understandings of mecha- nisms and impacts, it is important to take caution with the continued use of environmental compounds that disrupt male reproductive health. Importantly, continued studies are required to monitor the use of the known compounds as well as to screen all chemicals for potential AR disrupting activity so that caution may be applied with their continued use.

## 5. References Cited

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