J Endocrinol Reprod 17 (2013) 1 : 19-30 **Review Article**

A brief overview of androgen receptor: Its structure, functions and role in health and disease

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Summary

The androgen receptor (AR) signalling axis plays a vital role in the development, function and homeostasis of the prostate. The classical action of AR is to regulate gene transcriptional processes successively via AR nuclear translocation, binding to androgen response elements on target genes and recruitment of, or crosstalk with, transcription factors. Dysregulation of androgen/AR signalling perturbs normal reproductive development and accounts for a wide range of pathological conditions such as androgen-insensitive syndrome, prostate cancer (PCa) and cardiovascular diseases. Prostate cancer (PCa) initiation and progression is also uniquely dependent on AR. Androgen deprivation therapy remains the standard form of treatment of advanced PCa. Recent research provides a much more detailed understanding of the role of AR in normal human development and physiology in relation to its structure and functions. This review discusses genomic and non-genomic actions of AR, as well as their co-regulators. In addition we also explore several clinically relevant aspects of the molecular biology of the AR in the pathogenesis of non-cancerous and cancerous diseases

Key words: Androgen; Androgen receptor; Co-regulator; Genomic action; Prostate cancer

Introduction

Androgens, the male sex steroids, are responsible for the development of the male phenotype during embryogenesis and for the achievement of sexual maturation at puberty. In adulthood, androgens remain essential for the maintenance of male reproductive function and behaviour. Apart from their effects on reproduction, androgens affect a wide variety of non-reproductive tissues such as skin, bone, muscle, and brain (Heemers et al., 2006). Androgens mediate their physiological responses in target cells by interacting with intracellular high affinity receptor i.e., Androgen Receptor (AR).Testosterone and 5α-dihydrotestosterone are the major form of endogenous androgen in human. Testosterone is the primary circulating form (~95%) and is mainly secreted by the Leydig cell of testes in response to luteinizing hormone (LH) stimulation. Also a small amount of testosterone is produced by other organs like adrenal cortex, liver and ovary. 5α-dihydrotestosterone is another most active androgen produced from testosterone through its enzymatic conversion by an important steroidogenic enzyme i.e., 5-α-reductase.

AR is a member of steroid and nuclear receptor superfamily, which includes mineralocorticoid-, glucocorticoid-, estrogen- and progesterone receptor (MG, GR, ER and PR) (Heinlein and Chang, 2002; Montgomery et al., 2001). These receptors are classified as class-I receptor of the nuclear receptor super-family and includes several other receptors like thyroid hormone receptor, retinoic acid receptor, peroxisome proliferators activated receptor and vitamin D receptor (Detera-Wadleigh and Fanning, 1994). It is hypothesized that the entire nuclear receptor super-family evolved from a single ancestor *via* gene duplications and exon shuffling, and existed 500-830 million years ago, time since first vertebrate appeared (Gu, 1998 ; Gurel and Livshits, 2003). This hypothesis was supported by the presence of nuclear receptor in lower organisms such as jellyfish (Cnidaria) (Whitefield et al., 1999; Thornton, 2000). Upon binding to androgens, testosterone and DHT, AR undergoes conformational change that affects AR-protein and AR-DNA interactions, and nuclear shuttling. AR function and regulation is integral to the development of many parts of the body, in addition to its major actions on male sexual and prostate-development (Nelson et al., 2002). It mediates cell proliferation, differentiation, apoptosis and metabolism in many tissues, and secretion of proteins such as prostate-specific antigen (PSA) within the prostate, thereby functioning as a pivotal protein ally in tissue maintenance and homeostasis (Nelson et al., 2002). In this review we discuss some of the recent developments on the fundamental aspects of AR structure and function. This has also been linked to the genomic and non-genomic

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functions of AR and their cross-talks with AR-interacting proteins (co-regulators). Finally, in the concluding part of the review, we explore the clinical aspects of AR and assess their contributions and significance to the development, progression, and treatment of PCa.

AR structural and functional elements

To better understand the role of AR in regulating the growth and survival of PCa cells it is important to have a better and comprehensive understanding of the key determinants of AR structure and function. As a classical transcription factor AR shares modular structure similar to that of other steroid receptors. Functional domains of AR comprises of poorly conserved N-terminal regulatory domain (NTD) that modulates transcriptional activation (McEwan et al., 2004; Liesbeth et al., 2012).), a highly conserved central DNA binding domain (DBD), a short hinge region (H) and a moderately conserved C-terminal ligand binding domain (LBD) that are responsible for ligand recognition and binding. A nuclear localization signal (NLS) spans the region between DBD and hinge region. Two forms of AR have been reported so far, AR-α (87 kDa) and AR-β (110 kDa) (Wilson et al., 1994). AR-α has truncated N-terminus which lacks the first 187 amino acids as compared to full length of AR-β (Fig. 1).

The NTD is the main effector region of AR and is mainly responsible for transactivation function and can activate transcription independently of androgen in LBD negative mutants (Dennis et al., 2012). This differs from other steroid hormone receptors whose activity is attenuated by deletion of the C-terminal LBD and suggests that the primary site for interaction of AR with co-activator molecules that amplify the transcriptional signal and mediate AR action is *via* the NTD.

The DBD, as its name suggests, recognises and binds promoters and enhancers of androgen responsive genes. The cysteine-rich DBD comprises of two zinc finger domains formed from three alpha helices and C-terminal extensions. A conserved motif (P-Box) within the first zing finger coordinates gene specific nucleotide contact within the DNA major groove (Schoenmakers et al., 1999; Helsen et al., 2012) while another conserved amino acid motif (D-Box) in the second zing finger stabilizes the DNA-bound receptor complex and also mediates dimerization of steroid receptor monomer (Umesono and Evans, 1989; Schoenmakers et al., 1999). Hinge region is located at the junction of DBD and LBD and spans approximately 50 amino acids and contains a bipartite nuclear localisation signal for AR nuclear import and important sites for phosphorylation, acetylation and degradation (Liesbeth et al., 2012).

Located at the carboxyl terminus of AR, the LBD mediates high affinity binding of AR to natural androgenic ligand i.e., DHT and testosterone. Crystal structure of AR-LBD in complex with DHT (Sack et al., 2001) reveals a canonical ligand binding pocket formed by the ordered arrangement of highly conserved 12 alpha helices which is thought to reduce ligand dissociation and increase ligand-activated transcription (Matias et al., 2000; Sack et al., 2001). A ligand dependent AF-2 function is located in LBD, and mutation of this region is found to dramatically reduce the ligand-dependent AR activation (Bevan et al., 1999). Since AR activation follows a series of protein-protein and protein-DNA interactions, which are initiated by ligand-induced conformational change, LBD remains an important target site for modulation of AR functions.

Genomic activity of androgen receptor

In the absence of ligands AR is located primarily in the cytoplasm where it is associated with heat shock proteins (HSPs) (He et al., 1999, 2000; Loyet et al., 2003, Sara et al 2012), cytoskeletal proteins (Veldscholteet al., 1992), and other chaperones (Ozanne et al., 2000; Loy et al., 2003). HSPs are believed to hold together AR in the cytoplasm via cytoskeleton proteins and modulate AR conformation in preparation for efficient ligand binding (Cardozo et al., 2003; Shatkina et al., 2003). Binding of the cognate ligands, i.e., testosterone or DHT to AR, induces a conformational change in AR where the ligand-binding domain (LBD) forms the activation function2 (AF2)-binding surface (Fig. 1) (Liao et al., 2003; Dennis et al., 2012). The AF2 ligand-binding surface integrates the LBD and amino-terminal (N) transactivation domain (NTD) (N/C interaction), by binding specific short amino acid sequence motifs within the NTD (He et al., 1999, 2002; Schaufele et al., 2005). The result of this conformational change is the dissociation of AR from HSPs, enabling AR to interact with co-regulators such as ARA70 (binds to AR-DBD and AR-LBD), Filamin-A, and importin, which bind to the AR nuclear localization signal (NLS). These interactions facilitate nuclear targeting of AR and consequent nuclear dimerization (Ozanne et al., 2000; Rahman et al., 2004; Schaufele et al., 2005; Cutress et al., 2008). AR functions most commonly as a homodimer but it has also been shown to form heterodimers with the orphan nuclear receptor, testicular

receptor 4 (TR4) and the ER isoform, providing variances in transcriptional regulation (Lee et al., 1999). AR is a substrate for kinase, and more precisely is the downstream target of receptor-tyrosine kinase (RTK), for example HER-2/neu, and G-protein-coupled receptor (GPCR) signalling, both of which can activate AR independently of androgen (Yeh et al., 1999; Manin et al., 2002; Cao et al., 2006).

AR activity is mediated by phosphorylation at several serine residues with or without a bound ligand (Gioeli et al., 2002). Androgen binding promotes kinase recruitment and phosphorylation at serine residues (Ser80, Ser93 and Ser641) that are believed to function by protecting AR from proteolytic degradation (Blok et al., 1998). AR genomic activity also relies strongly upon serine phosphorylation (Ser213, Ser506 and Ser650). Phosphorylation by the mitogen-activated protein kinase (MAPK), extracellular signal - regulated protein kinase (ERK), p38, c-Jun N-terminal kinase (JNK) or Akt (protein kinase B/PKB) also acts to enhance AR response to low levels of androgens, estrogens and anti-androgens and aids in recruitment of nuclear co-activators required for chromatin remodelling (Rochette-Egly, 2003). AR N/C interactions occur predominantly when ARs are mobile, possibly to prevent unfavorable or untimely co-factor interactions. These N/C interactions are largely lost when AR transiently binds to DNA (androgen response element) (van Royen et al., 2007; Denayer et al., 2010). AR binding to tissue specific AREs enables recruitment of histone acetyltransferase (HAT) enzymes, an array of co-regulators and the general transcription machinery, thereby triggering transcription of androgen-dependent genes such as PSA and probasin (He et al., 2002; Heinlein and Chang, 2002; Powell et al., 2004) (Fig. 2). The nature of AR-bound ligands determines the stability of AR-DNA complexes and, ultimately, translocates to the nucleus. However, AR-ARE binding stability and time are significantly reduced after ligand-AR intercation, resulting in reduced transcriptional activation (Farla et al., 2005; Klokk et al., 2007). Subsequently, loss of bound ligand allows the nuclear export signal (NES) to co-ordinate AR shuttling to the cytoplasm where AR can be tethered again to cytoskeletal proteins in preparation for ligand binding (He et al., 2002). Alternatively, AR can be targeted for proteosomal degradation, regulating AR-protein levels and, consequently, genomic and non-genomic activity. AR proteosomal targeting requires phosphorylation of specific residues for recognition by E3 ubiquitin ligase and is likely not mediated by a PEST (proline-, glutamate-, serine-, and threonine-rich) sequence located in the AR hinge region (Gaughan et al., 2005; Haelens et al., 2007). Thus, the mobility of AR and its role as transcription factor is well controlled in maintaining cellular health and homeostasis.

Non-genomic activity of androgen receptor

In addition to well-characterised genomic roles, evidences substantiating that AR also potentiates non-genomic signalling pathways, have mounted over the past 20 years. Both its genomic and non-genomic actions have been summarised in the figure 2. The non-genomic signalling by AR is characterised by speed, with response times being seconds to minutes, indicating a lack of transcription and translation from androgen-responsive genes. This action originates at the plasma membrane or in the cytoplasm, triggering release of intracellular calcium and activation of protein kinases such as MAPK (ERK), protein kinase A (PKA), Akt and protein kinase C (PKC) (Baron et al., 2004; Foradori et al., 2008; Li and Al-Azzawi, 2009). AR can interact directly with, numerous growth factor signalling molecules at the plasma membrane and stimulate the signalling cascades. AR-NTD interacts directly with the p85 regulatory subunit of phosphoinositide 3-kinase (PI3K), activating the key downstream effector molecule i.e., Akt. This non-genomic action of AR is initiated following androgen treatment. It does this by interacting with the Src homology 3 (SH3) domain of Src by rapidly stimulating Src kinase activity leading to ERK2 activation. Src and the MAPK signalling proteins, Shc and ERK1/2, can be found located in caveolae membrane structures (Okamoto et al., 1998). Caveolae are known to house many signalling proteins and membrane receptors. This interaction may be necessary prior to non-genomic AR activity originating from caveolae structures. The regions of AR that are responsible for genomic activities are distinct from the ones responsible for these non-genomic cascades (Kousteni et al., 2001). Differences arise in AR non-genomic signalling when comparing androgen-dependent and androgen-independent cell lines. In androgen-dependent LNCaP cells, activation of the Src/MEK/ERK/CREB pathway relies upon androgen stimulation. In contrast, constitutive activation of the same pathway in androgen-independent LNCaP cells has highlighted an AR-associated redundancy (Unni et al., 2004). Additionally, re-expression of AR in androgen-independent PC3 prostate cancer cell line interferes with epidermal growth factor (EGF) receptor signalling and internalisation and PI3K activation, inducing a less invasive phenotype (Bonaccorsi et al., 2004). However, in

androgen-independent LNCaP cells, AR can localise to caveolin-negative rafts and interact and activate Akt independently of PI3K, which is normally required for downstream activation of Akt (Cinar et al., 2007). In comparison, androgen-dependent LNCaP cells mediate EGF-induced signalling via Akt, but independenty of AR (Zhuang et al., 2002). Irrespective of the pathway and cell model investigated, AR non-genomic signalling appears to either contribute to or inhibit prostate cancer progression, which needs further validation. Individual cell-signalling fingerprints most likely exist for each cell line or cancer, giving the impression of contrasting AR non-genomic activity when actually individual cancers and cell lines cannot be compared directly with confidence. It is possible that AR non-genomic activity ultimately serves to influence AR genomic activity and that of other nuclear receptors. AR-activated kinases can phosphorylate AR, regardless of AR-ligand binding status, thus creating an autocrine positive feedback loop. Kinases such as ERK1/2, PI3K and Akt can phosphorylate and activate AR with and without androgen, illustrating the adaptive nature of AR genomic activity in environments with varying levels of androgen.

Androgen receptor co-regulators

AR co-regulators function as transactivation chaperones. They act upon AR with and without bound ligand in a variety of subcellular locations, influencing DNA binding, nuclear translocation, chromatin remodeling, binding interruption of other co-regulators, AR stability, and bridging AR with the basal transcriptional machinery. The number of co-regulators known to interact with AR is considerable and continues to grow (Heinlein and Chang, 2002; Chmelar et al., 2007; Dennis et al., 2012) with subsequent complication of transcription models for AR-regulated gene expressions. This part of the review partially presents information on only some of the AR co-regulators functioning as co-activators and co-repressors, since providing detailed information of these regulators is beyond the scope of this review.

Co-activators

Increased affinity of co-activators for AR is generally associated with ligand binding and primarily functions to enhance AR transactivation. SRC/p160 co-activators such as SRC-1, TIF2, and GRIP1 share a similar structural organisation and are able to recruit transcription factors and additional co-activators with HAT activity (Lemon and Tjian, 2000). These co-activators are characterised by three LXXLL motifs contained in the centre of their peptide sequence and a C-terminal glutamine rich region, both of which are used in nuclear receptor binding (Heinlein and Chang, 2002; McEwan, 2004). LXXLL-containing co-activators stabilise ligand-bound AR and thus enhance transactivation (Ding et al., 1998; Ma et al., 1999; Dennis et al., 2012). Co-activators containing HAT activity, such as cAMP response element binding protein (CREB)-binding protein (CBP)/p300 and p300/CBP-associated factor (p/CAF), interacts with AR to facilitate chromatin remodelling and responsible for linking AR with the transcriptional machinery (Shen et al., 2005). AR-associated (ARA) proteins are predominantly either co-activators (e.g., ARA24, ARA54, ARA55, ARA70, ARA160, ARA267) or co-repressor (ARA67) of AR, which are predominantly named according to their molecular weights, and do not show any structural or functional similarity. For example, the cytoplasmic ARA70 has roles in stabilising ligand-bound AR and enhancing ligand binding specificity, both of which ultimately enhance AR transactivation (Glass and Rosenfeld, 2000; Heinlein and Chang, 2002).

Co-repressors

Contrary to their activating counterparts, AR co-repressors function to inhibit transcription initiation from androgen-responsive genes. Two well-characterised examples are nuclear receptor co-repressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT). SMRT interacts with the NTD and LBD in both presence and absence of ligand (agonist or antagonist) while NCoR does so only in the presence of agonists (Cheng et al., 2002; Heinlein and Chang, 2002; Liao et al., 2003). Both SMRT and NCoR-mediated AR repression involve disruption of N/C interaction and competition with SRC/p160 co-activators (Liao et al., 2003; Wang et al., 2005; Perissi et al., 2010). SMRT and NCoR recruit histone deacetylases (HDAC), which promote DNA packaging into nucleosomes, preventing the basal transcription machinery and transcription factors or nuclear receptors from accessing promoter or enhancer regions and, thus, repressing transcription (Liao et al., 2003).

Androgen receptor and its role in health and disease

Role of AR in malignant disease

AR and prostate cancer

PCa is the third most common cancer and the second leading cause of cancer-related death for men in Western Countries (Foradori et al., 2008; Sara et al., 2012). AR plays a crucial role during PCa development

and has been found to be a principal driver of disease initiation and progression (Siddique et al., 2011; Blueman and Nelson, 2012). However, some exceptions have been reported where prostatic tumors have been shown to be independent of AR signalling (Parray et al., 2012; Blueman and Nelson, 2012). The initial stage of PCa is dependent on androgen and can be managed by a series of therapies that are antagonistic to AR or suppress AR signalling (Parray et al., 2012). However, the success of these therapies is temporary and, after a short remission period, tumors reappear as castration-resistant prostate cancer (CRPC). Recently, it has been observed that over-expression of AR is the most common event associated with CRPC (Parray et al., 2012; Blueman and Nelson, 2012). Multiple mechanisms activate AR in PCa cells during CRPC emergence (Parray et al., 2012). These include ligand independent activation of AR in an androgen-depleted environment, AR gene amplification and over-expression of AR co-activators (Golias et al., 2009; Parray et al., 2012). There is some consensus that even after androgen ablation therapy a low concentration of androgens released from adrenal gland and biosynthesized within tumors sustains the active AR signalling in CRPC patients (Cai et al., 2011). The detection of AR splice variants in CRPC disease has given another important dimension to the significance of AR during this disease (Dehm and Tindall, 2011; Watson et al., 2010). Though LBD is absent in AR splice variants, they yet exhibit higher AR transcriptional activity in PCa cells (Watson et al., 2010; Dehm and Tindall, 2011). The molecular mechanisms through which functionally active AR splice variants arise during progression of disease are not well known. It has been reported that splicing of exon within AR intron 2 introduces a stop codon upstream of exon 3 in the AR transcript that would encode an AR protein (lacking the second zinc finger of the DBD and LBD) if translated (Dehm and Tindall, 2011; Watson et al., 2010). It has been reported that AR splice variants activate genes involved in the metabolism of androgens and provide a survival advantage for cells in a low-androgen environment (Parray et al., 2012).

The transcriptional activity of AR is also affected by co-regulators that influence a number of functional properties of AR, including ligand selectivity and DNA-binding capacity. At the promoter region of target genes, co-regulators participate in DNA modification, either directly through modification of histones or indirectly by the recruitment of chromatin-modifying complexes, as well as functioning in the recruitment of the basal transcriptional machinery. These co-regulators can promote (co-activators) or inhibit (co-repressors) AR function. Because AR is generally expressed in prostate tumors and their metastases (van der Kwast et al., 1991), aberrant regulation of AR activity by co-regulators may contribute to prostate cancer progression or the acquired agonist effect of anti-androgens. For example, members of the Cdc25 family of dual-specificity phosphatases that activate cyclin-dependent kinases to enable cell cycle progression are differentially expressed in prostate cancer. Cdc25B has been shown to interact directly with AR in a ligand-dependent manner but independently of its cell cycle function.

AR and breast cancer

The most common cause of breast cancer disease progression and mortality is evading of ER signalling during development of endocrine resistance disease. A recent study showed that AR is expressed in 60-70% of breast tumors, independent of ER status. Androgens are reported to inhibit or stimulate cell proliferation in pre-clinical models of breast cancer (Ni et al., 2011). Molecular apocrine is a subtype of ER-negative breast cancer that is characterized by the over-expression of steroid-response genes such as AR (Hickey et al., 2012). Further, AR regulates extracellular signal-regulated kinase (ERK) phosphorylation and kinase activity in molecular apocrine breast cancer. Inhibition of AR results in the down-regulation of ERK target proteins such as phospho-RSK1, phospho-Elk-1, and c-Fos in breast cancer cells. This study also reported that AR-mediated induction of ERK requires ErbB2, and AR in turn regulates ErbB2 expression. These findings suggest that there is a positive feedback loop between AR and ERK-signalling in apocrine subtype of breast cancer. AR expression can also be used as an informative biomarker for breast cancer survival (Peter et al., 2012). Naderi et al. (2011) showed the synergistic action of AR inhibitor (flutamide) and MEK inhibitor (CI-1040) against the growth of apocrine breast cancer cells.

AR and salivary duct carcinoma

Salivary duct carcinoma (SDC) is a rare invasive malignancy arising in the ductal epithelium of the salivary gland which is characterized by its morphologic resemblance to ductal carcinoma of the breast. Although expression of ER in SDC disease is rare, the presence of AR has been reported by different studies (Fan et al., 2000; Moriki et al., 2001). AR is reported to be expressed in over 90% of SDCs. The immunophenotypic homology that exists between SDC and PCa suggests that antiandrogen therapy, which is used for the treatment of PCa, might also be beneficial in patients of metastatic

SDC disease (Fan et al., 2000). AR is reported to express significantly more often in SDCs of men (79%) than in SDCs of women (33%) (Williams et al., 2007). AR is expressed in a majority of SDC and is useful for the diagnosis of SDC disease (Moriki et al., 2001).

AR and hepatocellular carcinoma (HCC)

Recent reports suggest the contribution of AR in pathogenesis of HCC disease in humans. AR is expressed at high levels in HCC cell lines exhibiting high metastatic potential, and AR activation promotes the cell migration and invasion potential in these cells (Ao et al., 2012). AR activation has been shown to enhance the expression of metastasis-promoting gene, ID1, that leads to the increased invasiveness of HCC cells (Ao et al., 2012). Mice lacking AR develop more undifferentiated hepatic tumors with larger tumor size at the metastatic stage (Ma et al., 2012). Further, AR plays a crucial role in HBV-induced hepatocarcinogenesis in HBV transgenic mice (lacking AR only in the hepatocytes HBV-L-AR(-/y) (Wu et al., 2010). Mutant HBV-L-AR(-/y) mice exhibit lower incidence of HCC, smaller size of tumors, fewer number of foci, and less HCC markers such as alpha-fetoprotein than wild-type HBV-AR(+/y) littermates. This study thus suggests that AR could be developed as target for therapy to combat HBV-induced HCC.

AR and bladder cancer

Emerging evidences support the view that bladder cancer is a member of the endocrine-related tumors. Males are reported to have higher incidence of bladder cancer than females (Miyamoto et al., 2012; Shiota et al., 2012). Recent studies suggest that AR plays a crucial role in the pathogenesis of bladder cancer, and blockage of AR has been shown to decrease growth, colony formation and viability in bladder cancer cells (Miyamoto et al. 2012; Shiota et al., 2012). Miyomoto et al. (2012) showed that more than 92% of AR wild-type male and 42% of AR wild-type female mice treated with N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) eventually developed bladder cancer, whereas none of the male or female AR knockout (ARKO) mice did develop tumor (Miyamoto et al., 2012). This study showed that BBN treatment supplemented with DHT induced bladder cancer in ARKO mice and castrated wild-type male mice. Thus, this study establishes AR as a target for treatment of bladder cancer. UDP-glucuronosyltransferases (UGTs), major phase II drug metabolism enzymes, play an important role in urinary bladder cancer initiation by detoxifying carcinogens. A recent study showed that AR promotes bladder carcinogenesis by down-regulating UGTs in the bladder (Izumi et al., 2011). Silencing of AR is reported to inhibit proliferation, apoptosis, and migration of human bladder carcinoma cell lines T24 and 253-J *in vitro* and suppress bladder tumor growth *in vivo* (Wu et al., 2010).

Role of AR in non-malignant disease

AR is reported to play role in several non-cancerous diseases in men and women (Fig. 3). The most common clinical symptoms of androgen deficiency in humans are the reduction of sex motivation, sex arousal, vaginal vasocongestion, reduction of pubic hair, bone mass, muscle mass, worsening of quality of life (mood, affect, energy), frequent vasomotor symptoms, insomnia, depression and headache (Jakiel and Baran, 2005). Hyperandrogenemia is the most consistent feature of polycystic ovary syndrome (PCOS), and AR is reported to play an important role in PCOS pathogenesis in women (Skrgatic et al., 2012). Studies conducted in transgenic/knockout mouse models showed that aberration in AR signalling impairs critical functions such as follicular maturation, fertility, brain patterning and sexual behavior (De Gendt et al., 2012). Irregular androgen levels have been shown to have a positive correlation with metabolic syndromes such as acne, hirsutism and virilization in humans (Lai et al., 2012). Furthermore, antiandrogen therapies are generally recommended to ameliorate hirsutism commonly observed in PCOS patients (Eagleson et al., 2000; Gambineri et al., 2004). Reports have shown that administration of anti-androgens restores ovulation in subsets of women (Eagleson et al., 2000; Gambineri et al., 2004). It has been shown that AR plays a crucial role in adrenal virilism, characterized by excess production of androgens, cortisol, or mineralocorticoids (Holterhus et al., 2002). AR activation is reported to play a role in endocrine disorders in children such as precocious puberty (Zaya et al., 2012). A recently published comprehensive review by Lai et al. (2011) has shown the role of androgen/AR in acne vulgaris (cystic acne or simply acne), androgenetic alopecia/alopecia androgenetica (hair loss), hirsutism (overproduction of androgens or increased sensitivity of hair follicles to androgens in females), and cutaneous wound healing.

Conclusion and future prospects

Taken together, the information discussed above provides considerable understanding of the physiological and pathological roles of AR. Although knowledge of AR structure, functional mechanisms within cells, and

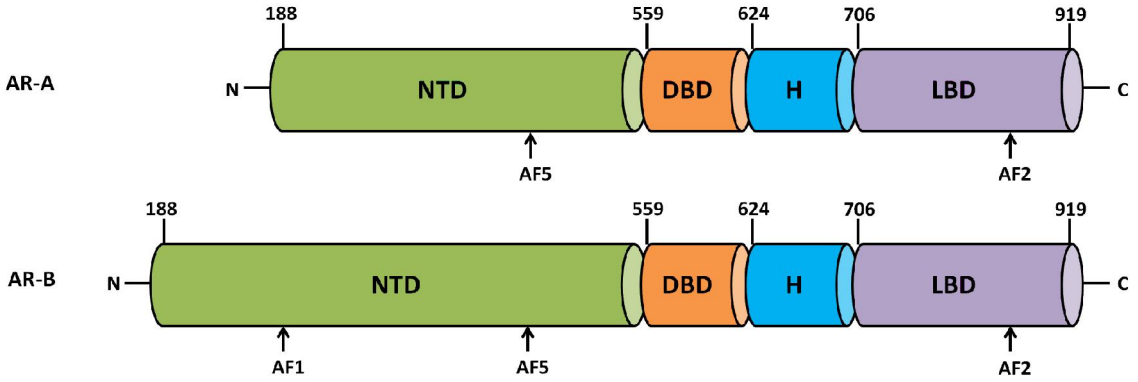

Fig. 1. Schematic overview of the different functional domains of two isoforms (AR-α and AR-β) of the human androgen receptor. Numbers above the bars refer to the amino acid residues which separate the domains starting from the N-terminus (left) to C-terminus (right). NTD, N-terminal domain; DBD, DNA-binding domain; LBD, ligand-binding domain; AF, activation function.

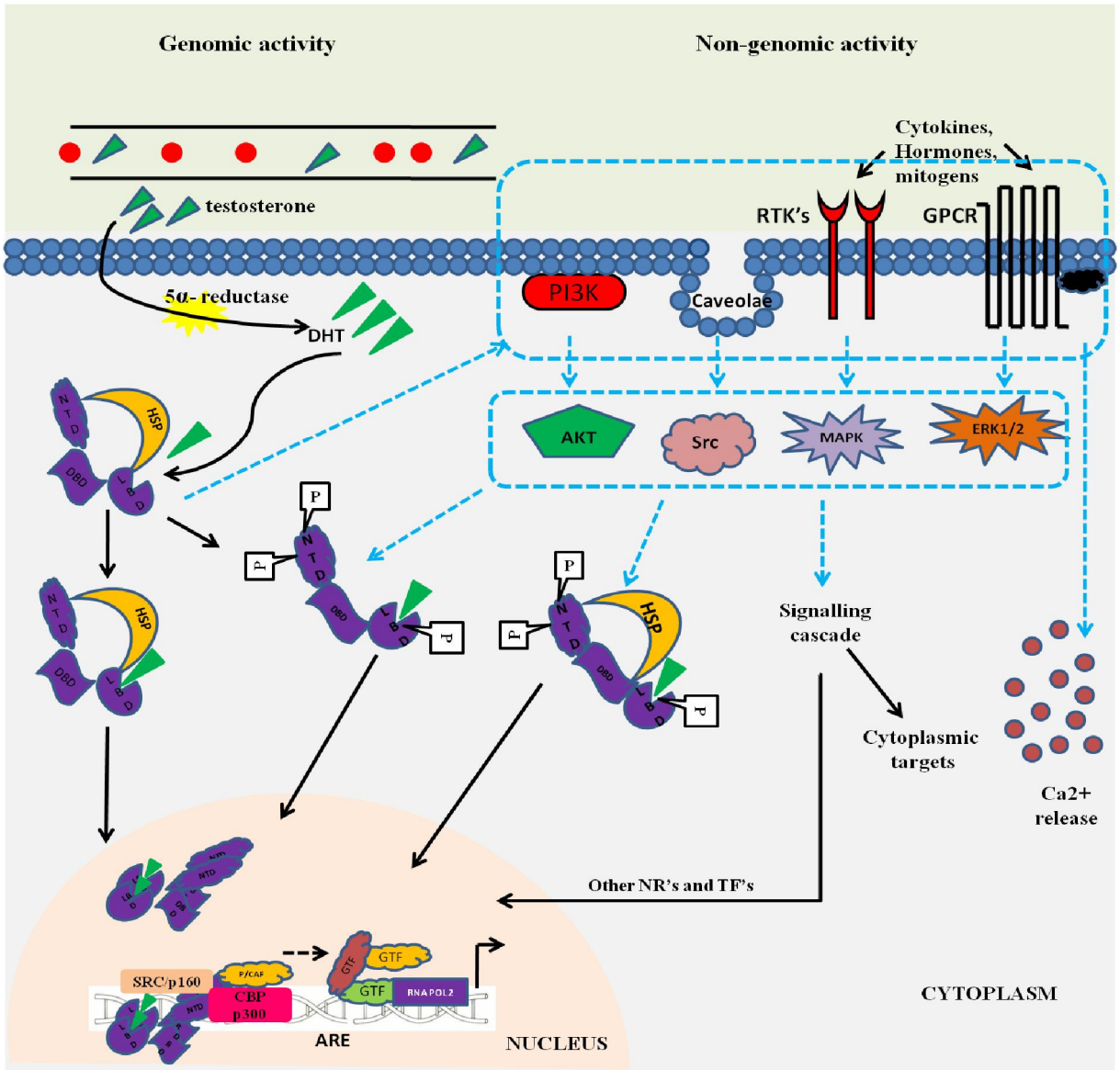

Fig. 2. Genomic and non-genomic actions of androgen receptor (AR). AR (purple) is illustrated as a modular protein with each of its domains represented; NTD (N-terminal transactivation domain), DBD (DNA-binding domain), the hinge and the LBD (ligand-binding domain). Non-genomic pathway of AR is highlighted in broken lines.

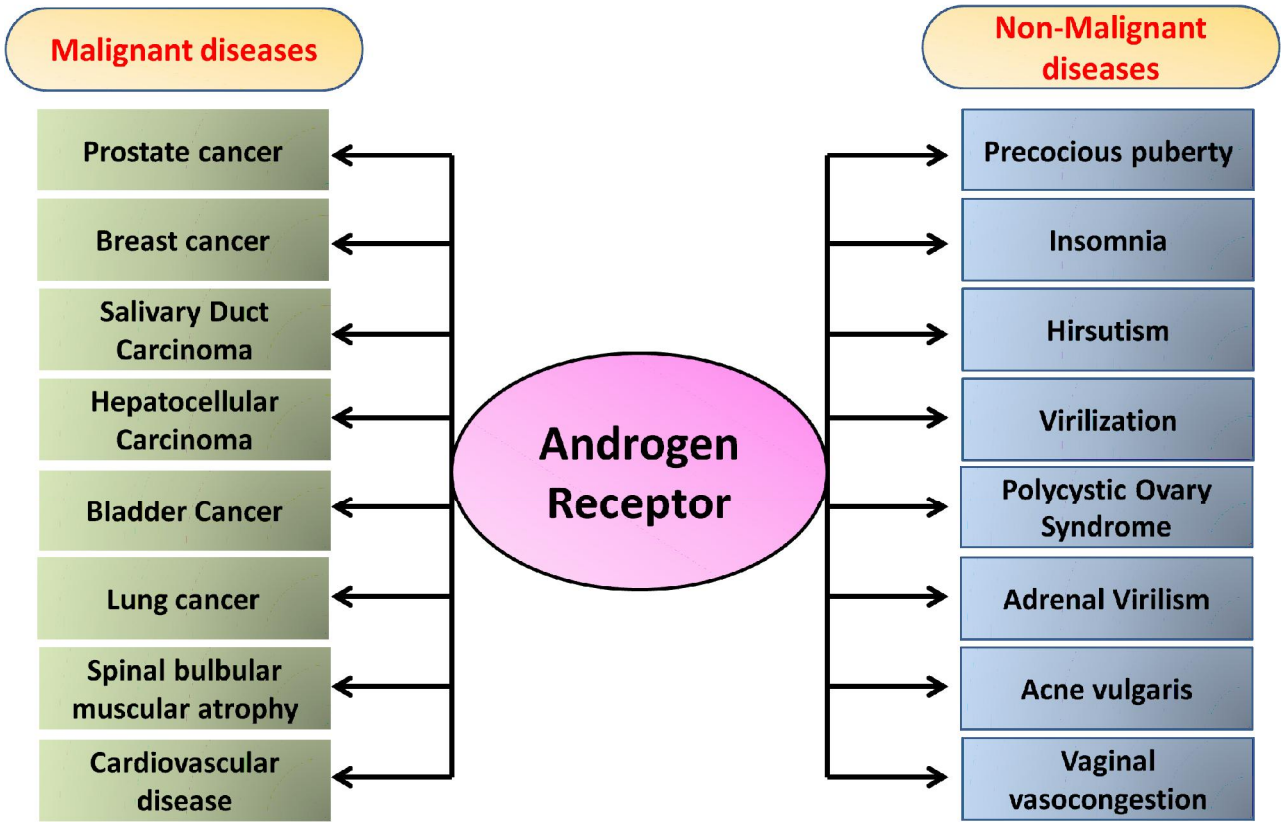

Fig. 3. The figure depicts the role of androgen receptor in human malignant and non-malignant diseases.

molecular biology is extensive, certain aspects of AR still need to be characterised. For example, detail regarding AR transcriptional regulatory complexes and AR non-genomic regulatory complexes and their functional role/s is not yet well understood. AR co-regulators or interacting proteins are discovered primarily through yeast two-hybrid analyses, Far Western-assays, GST pull-down assays, and ChIP assays. While these techniques have a proven track record for identifying interacting partners, they are limited by their ability to identify only one interacting partner at a time. Molecular and animal/clinical studies provide an understanding of how the androgen-AR signalling pathway plays key roles in the physiological and pathological processes. However, many questions pertaining to the precise mechanisms underlying androgen-AR signalling pathway remain to be addressed. Hence, further elaborate studies are needed to gain complete understanding of modes of action of AR, which would greatly impact clinical practices.

Acknowledgments

The authors would like to thank Department of Biotechnology (No. BT/PR14836/AAQ/01/455/2010), and Council of Scientific and Industrial Research (No. 37(1402)/10/EMR II dated 12/04/2010), Government of India, for financial support as funded projects.

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