



Androgen Signaling: Promising Target for Prospective Cancer Therapy

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Abstract

Androgen is a steroid hormone that triggers or controls the development and maintenance of male sexual characteristics through their association with nuclear transcription factor known as Androgen Receptor (AR). AR signaling cascade mechanism plays a critical role in the growth and development of male and female reproductive organs, but the latter to a lesser extent. During recent years, abnormal amplification of androgen gene and dysfunction of AR gene expression have been shown to be associated with wide range of malignancies in humans including prostate cancer, bladder cancer, esophageal cancer, neuroblastomas and also certain types of breast cancers in females. Therapies including administration of antiandrogens, deprivation or ablation of androgens, use of androgen receptor antagonist and androgen synthesis inhibitors have been successfully implemented in the treatment of androgen-dependent conditions in both males and females. However, the treatment failure associated with these therapies due to robust acquired resistance development by malignant cells has led to increased mortality, especially in Castration-Resistant Prostate Cancer (CRPC) patients. This mini review article summarizes different androgen related pathologies and list molecules that have been proved to be effective in treating androgen associated malignancies. Further, this article also identifies the benefits and discusses the challenges and opportunities of discovering new drugs targeting androgen and AR regulated mechanisms in cancers therapeutics.

Keywords

Steroid hormone, Androgen, Androgen receptor, Antiandrogen, Antagonist, Cancer therapy

Introduction

Androgens are a class of steroid hormones in humans controlling the development and maintenance of male sexual characteristics [1]. Testosterone and Dihydrotestosterone (DHT) are the most common androgens found in vertebrates that plays an equivalent role in male sexual development. In general, testosterone is converted to DHT and 17 β -estradiol (E2), the main active estrogen by 5 α -reductase type- 1/2, 3-oxo-5 α -steroid 4-dehydrogenase- 1/2 (SRD5A1/2) and aromatase [2]. Other androgens in vertebrates include Dehydroepiandrosterone (DHEA), Androstenedione (A4) and Androstenediol (A5). Androgens mainly regulate the growth and sexual characteristics by binding to nuclear receptor super family transcription factor known as Androgen Receptors (AR). AR signaling is highly important in vertebrates for prostate, sexual and physiological development [3]. Androgen stimulates growth of reproductive tract and

induces differentiation of epididymis, seminal vesicles, and vas deferens. At the onset of male pubertal changes, androgens play important role in enlargement of larynx and thickening of vocal cords that deepens male voice. Androgens possess anabolic effects on bone tissues and skeletal muscles. They modulate distribution of subcutaneous fat and play critical role in libido development [2]. Androgens have also been shown to modulate the activity and/or expression of drug detoxifying enzymes

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such as cytochrome P450 (e.g., cytochrome P450, family 4, subfamily B, polypeptide 1) and Uridine 5'-diphospho-glucuronosyltransferase (e.g., UDP Glucuronosyl transferase Family 1 Member A subtype) through AR signaling pathways [1].

Androgen Receptor (AR) is a member of steroid and nuclear receptor super family expressed at very low levels in many human tissues [4]. The AR has a molecular weight of 110 Kd, which composed of 919 amino acids. The gene encoding AR in human is located on the X-chromosome (Xq11-12) and it is formed of 8 exons and 7 introns [5]. AR is a transcription factor that can be activated by binding of specific ligands such as testosterone and 5-dihydrotestosterone. AR protein has 3 domains: (a) Ligand-Binding Domain (LBD) that binds to androgens and antiandrogens, (b) DNA-Binding Domain (DBD) that binds to Androgen Response Elements (AREs) present in the enhancers and promoters of target genes and, (c) N-Terminal Domain (NTD) that contains Activation Function-1 (AF-1), which is responsible for most of the AR's transcriptional activity. The NTD is an unfolded domain, which is highly disordered. Therefore, targeting NTD domain for drug development is extremely difficult. AF-1 comprises of two transcriptional activation units: Tau1 and Tau5, which are essential for transcriptional activation of both Full-Length AR (FL-AR) and constitutively active AR splice variants lacking the LBD. The hinge region of AR contains a Nuclear Translocation Sequence (NTS) that import AR into cell nucleus by nuclear transport [4,6]. In the absence of androgen, inactive AR is localized in the cytoplasm where it forms an association with a Heat Shock Protein (HSP)90 chaperone complex that undergoes proteasome-mediated

degradation [2]. However, in the presence of androgen, AR becomes hyperphosphorylated, then translocated to the nucleus and undergoes dimerization. After dimerization, AR interacts with other co-regulatory proteins and transcriptional machinery on AREs of target genes to initiate transcription [4]. AR has also been known to induce apoptosis at certain conditions. Several regulators such as Breast Cancer Genes 1 (BRCA1), Smad3 and serine-threonine kinase Akt (protein kinase B) regulate androgen-mediated apoptosis. The abnormal amplification of androgen gene and dysregulation of AR gene expression have resulted in wide range of malignancies in humans. Thus, targeting androgen and AR signaling cascade would open up new doors to treat androgen dependent malignancies in humans.

Role of Androgen in Different Cancer Types

An abnormal expression of androgen and AR have been implicated in wide range of pathologies including prostate cancer, breast cancer, esophageal cancer, neuroblastomas, bladder cancer and salivary gland cancer (Figure 1).

Prostate cancer

The prostate requires optimal levels of steroid androgens and AR for maintenance of its architecture and function [7]. Testosterone and DHT plays major role in the activation of growth factors by influencing cell signaling through AR. Normal prostate can be transformed into benign prostrate hyperplasia or prostatic cancer under very high levels of androgen [8,9]. It has been reported earlier that prostate cancer occurs rarely in eunuchs or in men deficient in 5 α -reductases, a key enzyme that

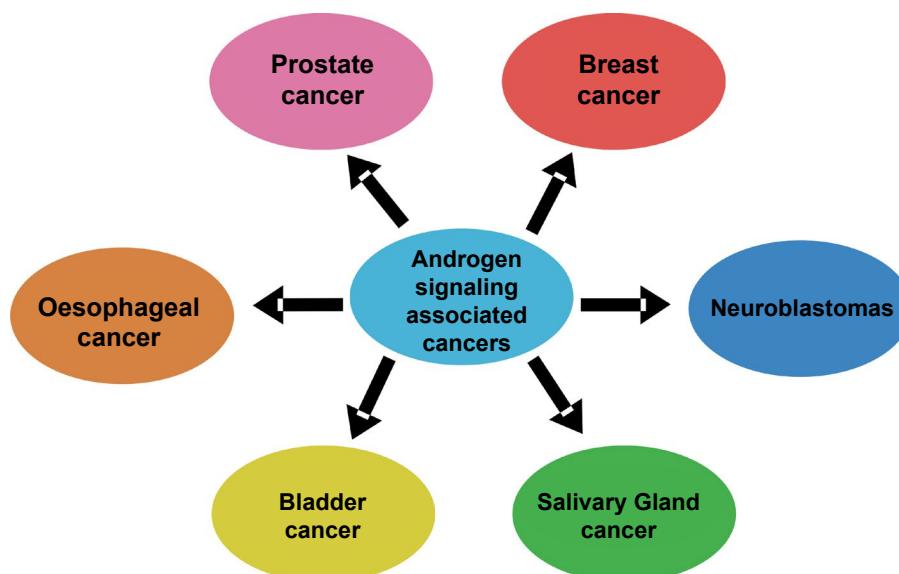


Figure 1: Androgen signaling associated pathologies in humans. An abnormal expression of androgen and AR have been associated in wide range of cancers in human including prostate cancer, breast cancer, oesophageal cancer, neuroblastomas, bladder cancer and salivary gland cancer.

converts testosterone to 5 α -dihydrotestosterone [10]. The Prostate-Specific Membrane Antigen (PSMA) is expressed in 90% of prostate carcinomas. PSMA is a type II transmembrane protein with glutamate-carboxypeptidase activity, which showed several biological features with target structure more appropriate for ligand development for nuclear medicine. It serves as an excellent target for diagnosis and therapy owing to its high specificity at an undifferentiated stage. AR regulates Prostate-Specific Antigen (PSA) expression in prostate cancer cells. Earlier studies have also shown that the suppression of AR signaling pathways induced apoptosis in prostate cancer [3]. Androgens help in survival and proliferation of both benign and malignant prostate epithelial cells. Thus, the patients are routinely treated using Androgen Deprivation Therapy (ADT), either via orchiectomy (surgical castration) or Luteinizing Hormone-Releasing Hormone (LHRH) agonist/antagonist (chemical castration) to reduce the levels of androgen in blood [11]. ADT reduces serum testosterone to castrate levels with a testosterone concentration of < 20 ng/dl. Surgical castration has shown to drop the testosterone levels upto 15 ng/dl. Despite ADT, prostate cancer cells survive and grow through androgen independent mechanisms [12]. In prostate cancer, AR gets accumulated within nucleus in the presence of androgens [13]. ADT alone or in combination with docetaxel chemotherapy is initially effective in majority of the patients, but in some, the disease progresses to an incurable stage called Castration-Resistant Prostate Cancer (CRPC) [11].

Castration Resistant Prostate Cancer (CRPC)

Most patients with persistent AR signaling eventually progress to fatal condition known as Castration-Resistant Prostate Cancer (CRPC) [14]. AR contributes to resistance mechanisms in CRPC patients through AR amplification (increase in androgen sensitivity and antagonist-agonist conversion), AR mutations (gain of function mutations, recurrent point mutations in the LBD like L702H, W742C, H875Y, T878A and AR promiscuity), AR Variants (ARVs) (LBD deficient, ARV7 types resistant to abiraterone or enzalutamide and ARVs independent of androgens), AR activation by growth factors [i.e., Insulin-like Growth Factor-1 (IGF-1), Keratinocyte Growth Factor (KGF) and Epidermal Growth Factor (EGF)], receptor tyrosine kinase-activated pathway, AKT pathway, Prostate Cancer Non-Coding RNA1 (PCNCR1) dependent mechanisms, ligand-independent activation of AR by cAMP-dependent protein kinase and IL-6 pathways, increased expression of AR coactivators and intratumoral *de novo* synthesis of androgens [12,15].

CRPC patients showed a continuous increase in serum PSA levels despite castrate levels of testosterone. CRPC remains incurable with survival of patients for 2

to 3 year. CRPC patients have genetic aberrations that resides with AR (63%), tumor protein p53 (54%), ETS family (57%) and Phosphatase and Tensin Homolog (PTEN) (41%). In CRPC patients, androgens levels within the prostate remain high and support tumor growth survival via androgen-regulated genes. In CRPC cells, DHT is produced either by the classical pathway (or) backdoor pathway (or) 5 α -dione pathway. There is also a feedback loop that exists between miRNAs and AR signaling. It has been shown in tumors and serum of CRPC patients that androgens induce miR-21 expression through AR complex and positive feedback loop through PTEN [11]. Increase in Aldo-Keto Reductase family 1 member C3 (AKR1C3), 17 β -Hydroxysteroid Dehydrogenase type 3 (17 β HSD3) levels and decrease in Steroid 5 Alpha-Reductase 2 (SRD5A2) levels have been demonstrated in clinical and metastatic CRPC samples. Metastatic Castrate Resistant Prostate Cancer (mCRPC) has been shown with notable increase in the levels of Fatty Acid Synthase (FASN), Cytochrome P450 17A1 (CYP17A1), 3 β HSD1, and 3 β HSD2 genes in comparison with primary prostate cancer [16].

DHT synthesis has been shown to be associated with increased levels of hydroxy-delta-5-steroid dehydrogenase, 3-beta- and steroid delta-isomerase 1/2 (HSD3B1/2), 3-oxo-5 α -steroid 4-dehydrogenase 1 (SRD5A1) and AKR1C3. HSD3B1 and HSD3B2 encode for two isoenzymes responsible for the conversion of DHEA to AD. Aromatase is highly overexpressed in CRPC that converts AD and testosterone to estrogens suggesting its role in resistance mechanisms [17]. The aldo-keto reductase has been shown to be involved in intratumoral steroidogenesis [16]. Humans contain four AKR1C isoforms that reduces 5 α -DHT to 3 α -diol. AKR1C1 is a 20-ketosteroid reductase that forms 20 α -hydroxyprogesterone and inactivates progesterone. AKR1C2 is a 3-ketosteroid reductase that solely reduces and converts 5 α -DHT to 3 α -diol. AKR1C3 is a 17-ketosteroid reductase that converts Δ 4-androstene-3,17-dione to testosterone and estrone to 17 β -estradiol. AKR1C4 is a liver specific 3-ketosteroid reductase [18]. Human Aldo-Keto Reductase family 1 member C3 (AKR1C3) was initially identified as an enzyme in reducing 5 α -dihydrotestosterone (5 α -DHT) to 5 α -androstane-3 α , 17 β -diol (3 α -diol) and oxidizing 3 α -diol to androsterone. AKR1C3 has been found in testis and prostate [17].

Breast cancer

Estrogen and its Receptor (ER) have been known to play a pivotal role in breast cancers. ER α -positive diseases accounts for majority of breast cancers. The adjuvant therapy for breast cancer includes, use of antiestrogen (tamoxifen) or aromatase inhibitors. During recent years, Androgen and its Receptor (AR) have been report-

ed to be involved in breast cancer [19]. Androgen can influence breast cancer cell growth by aromatization of estrogens. There is a significant correlation existing between the blood androgen levels and breast cancer risk in premenopausal and postmenopausal women [20]. AR was found to be co-localized with ER α in breast cancer tissues that depicted the nuclear interaction of AR in ER α signaling. However, different subtypes of breast cancer have androgen receptor signaling without the co-operation of estrogen receptors. Thus, the clinical role of AR in primary breast cancer varies in different subtypes of breast cancers. In ER α negative cancers, Human Epidermal Growth Factor Receptor 2 (HER2) expressions has been found along with high expression levels of AR [21]. Triple Negative Breast Cancer (TNBC) is another type of breast cancer negative for ER α , Progesterone Receptor (PR) and HER2. At some exceptional cases, TNBC was found to be positive for AR. AR-positive breast cancer is more likely to be associated with Phosphatidylinositol-4,5-bisphosphate 3-Kinase, Catalytic subunit Alpha (PIK3CA) mutation, but has no association with P53 mutation. Previous reports have shown that AR-positive TNBC is more likely to have activation of Epidermal Growth Factor Receptor (EGFR) and Platelet-Derived Growth Factor Receptor (PDGFR β), and enriched for PIK3CA mutations [22]. The studies using DHEA androgen have given a very different perspective on its role in breast cancer. DHEA has been shown to decrease the secretion of IL-12 p70, sIL-2ra, IL-1a, IL-6 and IL-8 in cell lines MDA-MB-231, MCF-7 and ZR-75-30. IL-1ra and IL-1b were diminished in MDA-MB-231 and ZR-75-30 cells exposed to DHEA, while IL-2 decreased in MCF-7 and MDAMB-231 cells. Interestingly, DHEA has also been shown to greatly reduce the secretion of Vascular Endothelial Growth Factor (VEGF) in MCF-7 cells. DHEA has also been shown to decrease the migration and invasion of MCF-7 [23].

Esophageal cancer

Gastrointestinal tissues are not usually considered to be targets for steroid hormones. However, the function of AR in these tissues is largely unknown. Certain studies have reported AR expression in patients with colon adenocarcinoma. In Esophageal Squamous Cell Carcinoma (ESCC), AR expression did not correlate with patient age or tumor location, but rather it correlates well with other factors like gender, tumor differentiation, invasion and status of lymph node metastasis. Mutations have profound effect on AR signaling mechanisms. A short (GGC) n allele mutation found in South African men showed increased AR activity, which would best explain the risk of Oesophageal cancer in men with this mutation. Some patients with Esophageal Adeno Carcinoma (EAC) have shown positive results for AR upon staining

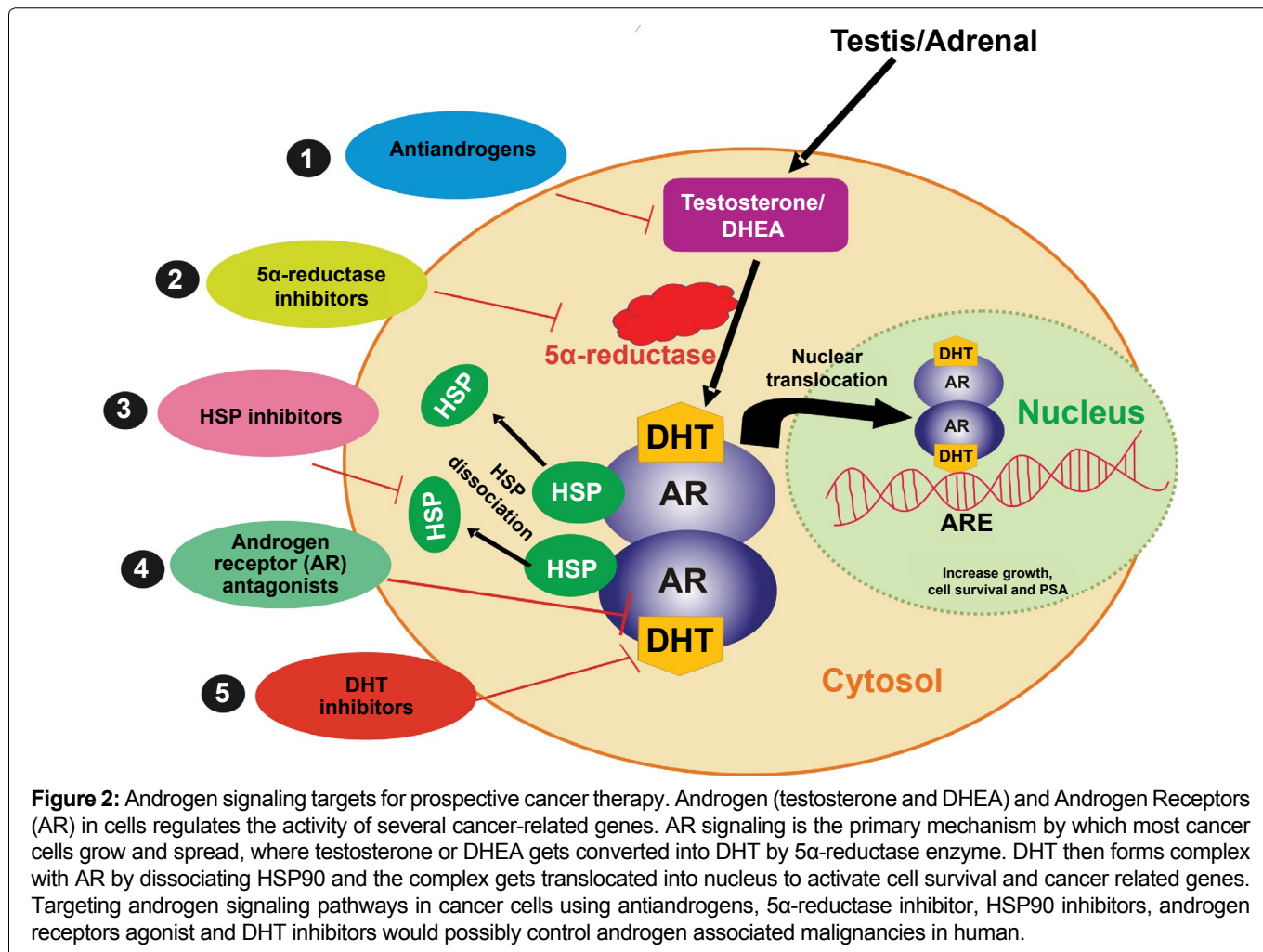
the cell stroma. This level has been decreased after surgical removal of cancer indicating the involvement of androgen in the pathogenesis and progression of diseases [24].

Neuroblastomas

Neuroblastoma (NB) is the most common extracranial solid tumor causing 15% of fatalities in children. Primary site of NB is retroperitoneum. The patients with neuroblastoma generally show aggressive local growth and metastasize of tumor to regional lymph nodes, liver, bone marrow, and bone cortex. The incidence of NB has been shown to be slightly higher in males than females. Despite major advances in therapies, neuroblastoma is still associated with a high morbidity and mortality. During recent years, androgen (R1881) has been reported to increase the proliferation and migration of neuroblastoma cells. However, the molecular pathogenesis underlying NB is not extensively studied. Previous studies have shown that use of androgen receptor antagonists such as enzalutamide (MDV3100) and Apalutamide (ARN509) decreased the proliferation of neuroblastoma cells suggesting the role of androgen and AR in neuroblastoma formation and disease progression [25].

Bladder cancer

Male internal genitalia (prostate, bulbourethral gland and urothelium) are generally derived from the urogenital sinus endoderm. AR has been shown to present in urothelium and bladder submucosa, where it regulates urine storage and urinary tract functions. AR signaling plays major role in high-grade prostatic intraepithelial neoplasia and prostatic adenocarcinoma. In addition, abundant expression of GATA Binding Protein 3 (GATA3), a zinc-finger transcription factor in urothelial cells also contribute to urothelial cancer along with AR. Loss of GATA3 expression in a subset of bladder cancers occur due to AR over expression or androgen treatment. Thus, androgens have been shown to induce growth of AR-positive bladder cancer cells [1]. Previous studies have shown that AR knockdown inhibited cell proliferation of bladder cancer lines grown in presence of androgens. Androgen-mediated AR signaling induced epithelial-to-mesenchymal transition. They also modulate the expression of Slug and activity of β -catenin/Wnt signaling in bladder cancer cells. Earlier reports have shown that AR and β -catenin co-expressed at the nuclei of bladder cancer cells and forms a complex with T-cell factor in the presence of androgens. Further, AR expression in bladder tumors was also found to be enhanced by co-activators like Nuclear Receptor Co-Activator 1, 2 & 3 (NCOA1, 2 and 3), CREB-binding protein, and E1A-associated Protein p300 (EP300). Interestingly, expression of JmjC Domain-Containing Histone Demethylation



Protein 3A (JMJD2A) and Lysine (K)-Specific Demethylase 1A (LSD1) also know to mediate AR transactivation via histone-lysine demethylation mechanisms [1].

Salivary gland cancer

Salivary Gland Cancer (SGC) is a malignant condition that forms in the tissues of salivary glands. There are different types of SGC including Salivary Duct Carcinoma (SDC), Adenoid Cystic Carcinoma (ACC), Muco Epidermoid Carcinoma (MEC), secretory carcinoma and Polymorphous Low Grade Adenocarcinoma (PLGA). Based on Immunohistochemistry (IHC) and RNA sequencing, SGS have been classified into AR IHC-positive and AR IHC-negative. AR IHC-negative SDCs are known to possess low levels of AR mRNA. In a few cases, AR IHC-negative and AR IHC-positive shared similar patterns of AR signaling with AR positive breast cancers. Adenocarcinoma (AC NOS) and Acinic Cell Carcinoma (AcCC) are AR-positive SDCs. It is interesting to note that only a small subset of MEC and ACC have detectable levels of AR expression, whereas PLGA and Basal Cell Adenocarcinoma (BCAC) showed rare expression of AR [26].

Drug Targets for Cancer Therapeutics

Targeting androgen and AR related mechanisms remains as the gold standard treatment for many different types of cancers (Figure 2). Antiandrogens are androgen antagonist that prevents activation of AR and cause tumor regression by competing androgen binding with AR Ligand Binding Domain (LBD) [4,26,27]. Bicalutamide, nilutamide, flutamide and enzalutamide are some of antiandrogen drugs used in tumor regression. Bicalutamide, nilutamide and flutamide are first-generation, whereas, enzalutamide is second generation antiandrogens [28]. Other AR targeted therapies include androgen ablation or androgen deprivation therapy, which suppress or block the production of male androgens. This can be achieved by orchiectomy or Luteinizing Hormone-Releasing Hormone (LHRH) agonists/antagonists, 17-ketosteroid reductase inhibitors or by down regulating the Gonadotropin-Releasing Hormone (GnRH) receptor signaling [29]. Triptorelin and goserelin are GnRH agonists, which down regulate the production of Luteinizing Hormone (LH) and reduced serum testosterone levels [26]. Abiraterone is a *CYP17A1* inhibitor that blocks the conversion of pregnenolone to

DHT. Abiraterone Acetate (AA) is a selective inhibitor of both 17 α -hydroxylase and c17, 20-lyase. It mainly targets adrenal and tumor intracrine androgen biosynthesis [28]. In many cancers, the conversion of inactive steroid hormone precursors to E2 is accomplished from sulfated estrogens (inactive) in the sulfatase pathways. Steroid Sulfatase (STS) enzymes in sulfatase pathway activate estrogen and estrogen sulfotransferase, which converts active Estrone (E1) and other estrogens to their inactive sulfates. Increased expression of STS in malignant tumor cells has been associated with increased levels of active estrogens that stimulate cell proliferation and cancer progression [30]. Therefore, targeting sulfatase pathways with STS inhibitors would also offer additional benefits in the cancer therapy. STS inhibitors combined with other androgen signaling inhibitors can effectively prevent cancer cell proliferation and progression.

Drug Resistance and Prospective Drug Development

In many tissues including the prostate, dihydrotestosterone or 5 α -dihydrotestosterone acts as the most active androgen. Therefore, targeting 5 α -reductase enzyme that catalyzes the reductive conversion of testosterone to 5 α -dihydrotestosterone would be the promising therapeutic target to treat androgen-dependent diseases in humans [31]. The mechanism of AR dependent resistance development in cancer cells include up regulation of AR, formation of AR splice variants, AR mutations and up regulation of Glucocorticoid Receptor (GR). GR up regulation in cancer cells is a potential resistance mechanism against the drug, enzalutamide [28]. Point mutations in AR are another mechanism of acquired resistance to abi-

aterone and next-generation AR antagonists (enzalutamide and apalutamide). The frequency of AR mutations in normal cells is lower; however, the frequency has been known to increase during advanced stages of disease due to therapy based selection of aberrant receptors. For instance, treatment with drugs such as bicalutamide and flutamide drives the selection of ARW741L/C and AR-H874Y/ART877A mutations in tumor cell growth [27]. AR-independent mechanisms include PI3K/AKT pathway activation (often resulting from loss of phosphatase and tensin homolog), tumor protein p53 mutations, Retinoblastoma (RB) protein loss, expression of Aurora Kinase A (AURKA) and proto-oncogene protein (N-Myc) alteration in DNA-repair genes [32]. Other pathways such as Phosphatidylinositol 3-Kinase (PI3K)/Protein Kinase B (PKB, also known as AKT), Ras/Mitogen-Activated Protein Kinases (MAPK), and Protein Kinase A (PKA) also contributed for cancer cell resistance to chemotherapy [33]. Previous studies have shown that androgens in prostate cancer cells have suppressed the expression of Protein Kinase D1 (PKD1) through fibroblast growth factor receptor substrate 2. Thus, PKD1 was identified as a novel androgen-suppressed gene, which could be potentially down regulated by androgen through a novel AR/FRS2/MEK/ERK pathway. Up-regulation of PKD1 by anti-androgens may also contribute to resistance development in prostate cancer cells [34,35]. Targeting PKD1 would be the other possible ways to treat prostate cancer. Thus, the treatment failures associated with current therapies warrants more intensive research to be conducted toward discovering novel therapeutic agents against androgens and AR related signaling mechanism. The molecules targeting androgen and AR related mechanisms are listed in Table 1.

Table 1: List of bioactive molecules/compounds targeting androgen and AR related mechanisms.

Molecule/compound	Nature of the molecule/compound	Targets	Mode of action	References
Niphatenone B	Glycerol ether initially isolated from the marine sponge <i>Niphates digitalis</i>	Androgen Receptor N-Terminal Domain	Inhibits transactivation of AR NTD, blocks endogenous expression of AR-regulated genes PSA and Kallikrein-2, covalent binding to AR AF-1 peptide.	Banuelos, et al. [4]
Sintokamide A	Natural compound isolated and purified from the marine sponge <i>Dysidea</i> sp.	AF-1 of Androgen receptor	Inhibits transactivation of AR NTD, attenuate transcriptional activities of both full-length AR and constitutively active AR splice variants AR-V567es, repressed androgen-induced levels of transcripts of FL-AR-regulated genes (KLK3/PSA, KLK2, TMPRSS2, NKX3.1, FKBP5, and SLC1A1).	Banuelos, et al. [6]
Isosilybin A	Flavolignan; one of the 7 components of Silymarin	Androgen receptor signaling	Decreases AR and PSA level in prostate cancer cells.	Deep, et al. [36]
Thiostrepton and Siomycin A	Thiazole antibiotics	AR signaling in neurons	Reduces expression of FOXM1 transcription factor and β -catenin, both required for localization and expression of AR.	Otto-Duessel, et al. [37]

Emodin	Antraquinone compound obtained from 50% ethanolic extract of <i>Polygonum multiflorum Thunb.</i> (Family: Polygonaceae)	5 α -reductase	Inhibits 5 α -reductase enzyme activity.	Cho, et al. [31]
6-(3,4-dihydro-1H-isoquinolin-2-yl)-N-(6-methylpyridin-2-yl)nicotinamide-26 (DIMN-26)	6-(3,4-Dihydro-1H-isoquinoline-2-yl)-N-(6-methoxypyridine-2-yl)nicotinamide-26	AR signaling	Inhibits Dihydrotestosterone (DHT) production, induce cell growth and proliferation, suppresses DHT-induced transcriptional activity and nuclear translocation of AR, binds to LBD (Ligand Binding Domain) of AR, reduced mRNA levels of PSA, AR, Ste20-related Protein Proline/Alanine-Rich Kinase (SPAK), Beta-2-Microglobulin (B2M), and Selenoprotein P1(SEPP1).	Choi, et al. [33]
Tocopheryl Quinone (TQ)	Oxidation product of alpha-tocopherol	Androgen receptor in prostate cancer cells	Decreases gene expression of TM4SF1, KLK2, FOXA1 and PSA.	Fajardo, et al. [38]
1,4-Substituted Triazoles	Non-steroidal antiandrogen	Androgen receptor in prostate cancer cells	Reduces the level of PSA.	Ferroni, et al. [39]
Darolutamide (ODM-20)	Non-steroidal antiandrogen	Androgen receptor of CRPC cells	Reduces serum PSA in CRPC and blocks nuclear translocation of AR.	Fizazi, et al. [40]
Zyflamend	Polyherbal preparation consisting of the supercritical CO ₂ fluid extracts of 10 different herbs	Androgen receptor in CRPC model	Reduces mRNA levels of AR and PSA.	Huang, et al. [41]
M-Mel	(1-(pyridine-2-yl)-3-(m-tolyl)imidazo[1,5-a]pyridine), a derivative of HIMP (3-phenyl-1-(pyridine-2-yl)imidazo[1,5-a]pyridine)	Androgen receptor of CRPC	Methyl group on the para position of the benzene ring in M-Mel suppress AR activity, decreases levels of PSA and p66Shc (a protein regulated by androgens).	Ingersoll, et al. [42]
Minnelide	Water soluble pro-drug of triptolide, a diterpene triepoxide isolated from a Chinese herb, <i>Tripterygium wilfordii</i>	Androgen receptor and its splice variants of CRPC	Induces apoptosis in androgen dependent and CRPC cells, inhibits AR transcription and downstream AR targets such as PSA and NKX3.1, prevents translocation of Sp1 to the nucleus (a transcription factor of AR).	Isharwal, et al. [43]
Decursin	Ethanol extract of herbal formula containing Korean <i>Angelica Gigas Nakai</i> (AGN) root and 9 Oriental herbs	Antiandrogen and androgen receptor	Suppression of PSA mRNA and protein, inhibits androgen-stimulated AR translocation to the nucleus, down-regulates AR protein abundance without interfering AR transcription.	Jiang, et al. [10]
Cyclopropane (1S,2R)-27	Thioether isostere	Nuclear androgen receptor	Reduction in PSA activity.	Johnson, et al. [14]
Lambertianic acid	Isolated <i>Pinus koraiensis</i> Siebold and Zucc (Family: Pinaceae)	Androgen receptor	Attenuates expression of AR and PSA.	Lee, et al. [3]
D4A	A converted form of abiraterone	Androgen receptor	Inhibits CYP17A1, 3 β HSD and SRD5A, required for DHT synthesis, AR antagonist, Inhibits DHT-induced AR chromatin occupancy on the PSA, TMPRSS2 and FKBP5 regulatory elements on chromatin.	Li, et al. [1]

Cryptotan shinone	Active extract of <i>Salvia miltiorrhiza</i> Bunge (Danshen), chemical name: (R)-1,2,6,7,8,9-Hexahydro-1,6,6-trimethyl-phenanthro(1,2-b) furan-10,11-dione	Androgen receptor in prostate cancer	Inhibits DHT-mediated AR transactivation, inhibits transcription of AR target genes (PSA, TMPRSS2, and TMEPA1), Inhibits AR N/C-Dimerization and formation of AR-coregulatory complex, blocked E2 or Adiol-mediated AR activity.	Xu, et al. [44]
AR1-558	Decoys of AR NTD residues 1-558	Androgen regulated genes	Reduces the expression of androgen-regulated genes HMGCR, KLK2, KLK3/PSA, MAF, RHOA, and SAT1, blocks AR-ARE interactions.	Myung, et al. [45]
Galeterone (ongoing clinical trials)	3 β -(hydroxy)-17-(1H-benzimidazole-1-yl) androstane-5,16-dione	Androgen receptor	CYP17 inhibition, AR antagonist and AR degrader.	Bastos & Antonarakis [46]
Compound 6m	2-(4-phenylthiazol-2-yl) isoindoline-1,3-dione derivative	Androgen receptor	Decreases androgen-mediated transcription of ARE-mRNA in PSA, TMPRSS2.	Saravanan, et al. [47]
NBBS (N-butylbenzene sulphonamide)	Dichloromethane extract from stem bark of <i>Pygeum africanum</i>	Androgen hormone	Inhibits AR mediated transactivation and androgen hormone induction.	Schleich, et al. [48]
Isobavachin, Glabranin, Anthocyanin and Eriosemation (via structure based docking studies)	Phytochemicals	Androgen receptor	AR antagonists.	Singh, et al. [49]
Flutamide	Non-steroidal drug	Androgen receptor in salivary duct carcinoma	Blocks DHT activity, inhibits invasion of DHT mediated cells.	Kamata, et al. [50]
CID 70128824, CID 70127147, and CID 70126881	7 α -substituted dihydrotestosterones by linear Quantitative Structure-Activity Relationship (QSAR) model (in-silico screening)	Androgen receptor antagonists or antiandrogens		Wang, et al. [51]
Metformin	Anti-diabetic drug, originally from <i>Galega officinalis</i> (French lilac)	Androgen receptor	Reduces mRNA and protein levels of AR.	Whitburn, et al. [13]
Diterpenoids T1 and its analogues T2 and T3	Furanoditerpenoid spongia-13(16), -14-dien-19-oic acid	Androgen receptor	Inhibits androgen-dependent proliferation and AR transcriptional activity, competes with androgen binding to LBD of AR and blocks essential N/C interactions.	Yang, et al. [15]
Combined Androgen Blockade (CAB); immediate switch from Bicalutamide to Flutamide	-	Prostate Specific Antigen (PSA)	Decreases the levels of PSA.	Yokomizo, et al. [52]
Acetyl-11-Keto- β -Boswellic Acid (AKBA)	Acetyl-11-keto- β -boswellic acid isolated from the gum-resin of <i>Boswellia carterii</i>	Androgen receptor in prostate cancer	Decrease DHT induced AR expression at both mRNA and protein levels, interruption of Sp1 binding activity, suppression of androgen induction of PSA promoter.	Yuan, et al. [53]
6-Bromoindirubin-3-Oxime (6BIO)	6-bromo-indirubin-30-oxime via small molecule high throughput screening	Androgen receptor and its signaling in prostate cancer	Down-regulates AR-V7 levels, a drug-resistance-related AR splice variant, enhanced ASO (Antisense oligonucleotides) function, represses AR expression by inhibition of two main Glycogen Synthase Kinase 3 (GSK-3) isoforms, GSK-3a and GSK-3b.	Zhang, et al. [54]

Conclusion

Ever since the role of androgen and AR signaling has been elucidated in wide variety of cancers, extensive research has been dedicated towards the discovery of next generation drugs from a myriad source, that specifically antagonize the AR signaling cascade, stop metastasis and proliferation of respective cancers. Multiple factors including age, type of cancer, status of metastasis and intensity of side effects, have to be taken into consideration while developing new therapeutic drugs for cancers. This article summarizes new molecules and compounds that have been successfully used and proved to decrease the expression of antigenic biomarker (PSA) and AR in cancer cells. The roles of AR have been clearly elucidated in prostate and breast cancer subtypes. However, more research need to be conducted on other cancer subtypes such as bladder cancer, salivary cancer, oesophageal cancer and neuroblastomas, in which the roles of androgens and AR have not been studied extensively. Therefore, understanding precise molecular mechanisms underlying androgen mediated malignancies would shed light on developing prospective targeted therapies to combat cancer. Future research efforts have been directed towards disrupting AR signaling axis, likely with small molecule inhibitors or by rational combinations of other potential targeted therapies, in order to make continued advances in our understanding of AR signaling mechanisms in different cancer subtypes, which would increase our ability to effectively treat androgen associated malignancies.

Conflicts of Interest

Authors declare no conflict of interest.

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