REVIEW

Increased androgen receptor transcription: a cause of castration-resistant prostate cancer and a possible therapeutic target

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Abstract

Few effective therapies exist for the treatment of castration-resistant prostate cancer (CRPC). Recent evidence suggests that CRPC may be caused by augmented androgen/androgen receptor (AR) signaling, generally involving AR overexpression. Aberrant androgen/AR signaling associated with AR overexpression also plays a key role in prostate carcinogenesis. Although AR overexpression could be attributed to gene amplification, only 10–20% of CRPCs exhibit AR gene amplification, and aberrant AR expression in the remaining instances of CRPC is thought to be attributed to transcriptional, translational, and post-translational mechanisms. Overexpression of AR at the protein level, as well as the mRNA level, has been found in CRPC, suggesting a key role for transcriptional regulation of AR expression. Since the analysis of the AR promoter region in the 1990s, several transcription factors have been reported to regulate AR transcription. In this review, we discuss the molecules involved in the control of AR gene expression, with emphasis on its transcriptional control by transcription factors in prostate cancer. We also consider the therapeutic potential of targeting AR expression.

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Introduction

The androgen/androgen receptor (AR) signaling pathway is known to play a critical role in prostate tumorigenesis and prostate cancer (PCa) progression. Androgen-deprivation therapy (ADT) either reduces the production of androgens by surgical or medical castration, or interferes with the activity of the AR through the use of anti-androgens (Miyamoto *et al.* 2004). ADT is initially effective in about 90% of PCa cases, but these eventually circumvent ADT and emerge as castration-resistant PCa (CRPC; Roy-Burman *et al.* 2005). However, the androgen/AR signaling pathway remains a key determinant of cell proliferation in CRPC, despite low levels of available androgens following ADT (Litvinov *et al.* 2003). The reactivation of the androgen/AR signaling pathway in CRPC has been attributed to a number of mechanisms, including AR hypersensitivity, local intracrine production of androgens, promiscuous activation of the AR by adrenal androgens, non-androgenic steroids and even anti-androgens, and activation of the AR by growth factors and cytokines (Debes & Tindall 2004, Titus *et al.* 2005). These phenomena may result from

abnormalities of the AR itself (AR mutation and overexpression) and/or its related molecules (AR cofactors). Furthermore, several kinds of AR splice variants displaying significant constitutive activity in the absence of ligand-binding have recently been reported by several laboratories (Dehm *et al.* 2008, Guo *et al.* 2009, Hu *et al.* 2009, Sun *et al.* 2010). Many studies have shown that progression to CRPC is associated with AR overexpression, and that AR inhibition represses tumor growth in PCa, even in CRPC (Gregory *et al.* 1998, Zagarra-Moro *et al.* 2002, Chen *et al.* 2004a,b, Scher & Sawyers 2005). Less than 10% of CRPC cases were found to possess somatic AR gene mutations (Taplin *et al.* 2003). In addition, the AR is upregulated in most CRPCs, of which only 10–20% exhibit amplification of the AR gene (Linja *et al.* 2001), indicating that increased AR expression in CRPC may result from factors other than gene amplification. The molecular mechanisms underpinning the aberrant AR expression have thus been intensively investigated as a potential source of novel therapeutic targets.

Although the expression of proteins, including AR protein, is regulated by various steps (transcription, translation, and post-translational control), the

Table 1 Transcription factor-related factors regulating human androgen receptor (AR) expression in prostate cancer

Factor	Gene classification	Gene function	Cells	Effect	Direct or indirect	Supposed mechanism	References
CREB	Transcription factor	Induction of genes in response to hormonal stimulation of the cAMP pathway	LNCaP	+	Direct	Binding to CRE site	Mizokami <i>et al.</i> (1994)
Myc	Transcription factor	Cell cycle progression, apoptosis, and cellular transformation	<i>Vitro</i>	+	Direct	Binding to E-box	Grad <i>et al.</i> (1999)
Myc	Transcription factor	Cell cycle progression, apoptosis, and cellular transformation	LNCaP	+	Indirect	Binding to E-box	Lee <i>et al.</i> (2009)
c-Jun	Transcription factor	Transforming gene	LNCaP	–	Direct	Binding to TRE site	Pan <i>et al.</i> (2003)
c-Jun	Transcription factor	Transforming gene	LNCaP	–	Direct	Binding to TRE site	Yuan <i>et al.</i> (2004)
Sp1	Transcription factor	Constitutive induction of genes	<i>Vitro</i>	+	Direct	Binding to GC-box	Faber <i>et al.</i> (1993)
Sp1	Transcription factor	Constitutive induction of genes	LNCaP	+	Direct	Binding to GC-box	Yuan <i>et al.</i> (2005)
p53	Transcription factor	Cell cycle arrest, apoptosis, senescence, DNA repair, and metabolism	LNCaP	–	Direct	Binding to p53-binding site	Alimirah <i>et al.</i> (2007)
Foxo3a	Transcription factor	Trigger for apoptosis	LNCaP	+	Direct	Binding to Foxo-response element	Yang <i>et al.</i> (2005)
LEF1	Transcription factor	Hair cell differentiation, follicle morphogenesis, and cellular transformation	LNCaP	+	Direct	Binding to LEF/TCF-binding site	Yang <i>et al.</i> (2006)
LEF1	Transcription factor	Hair cell differentiation, follicle morphogenesis, and cellular transformation	LNCaP, AI-LNCaP	+	Direct	Binding to LEF/TCF-binding site	Li <i>et al.</i> (2009)
Wnt-1	Cytokine	Oncogenesis and developmental processes	LNCaP	+	Indirect	Activation of β -catenin	Yang <i>et al.</i> (2006)
β -Catenin	Signal transduction	Cell growth and adhesion	LNCaP	+	Direct	Activation of LEF1 and LEF1 complex	Yang <i>et al.</i> (2006)
Pur α	Transcription factor	DNA replication and transcription	LNCaP, AI-LNCaP	–	Direct	Binding to suppressor element (ARS) binding sites	Wang <i>et al.</i> (2008)
NF κ B	Transcription factor	Cellular transformation and inflammation	LNCaP	+	Direct	Binding to NF κ B-binding site	Zhang <i>et al.</i> (2009)
Twist1	Transcription factor	Differentiation, epithelial–mesenchymal transition	LNCaP, 22Rv1, CxR	+	Direct	Binding to E-box	Shiota <i>et al.</i> (2010)
E2F1	Transcription factor	Cell cycle progression	LNCaP	–	Direct	Binding to E2F-binding site	Davis <i>et al.</i> (2006)
E2F1, E2F3	Transcription factor	Cell cycle progression	LNCaP	+	Direct	Binding to E2F-binding site	Sharma <i>et al.</i> (2010)
Rb1	Transcription cofactor	Cell cycle arrest and tumor suppressor	LNCaP, LAPC-4	–	Direct	Inhibition of E2F1 transactivation	Sharma <i>et al.</i> (2010)
SREBP-1	Transcription factor	Sterol biosynthesis	LNCaP, C4-2	+	Direct	Binding to sterol regulatory element	Huang <i>et al.</i> (2010)
β 2-Microglobulin	Membrane protein	Endocytosis of iron	LNCaP, C4-2	+	Indirect	Activation of SREBP-1	Huang <i>et al.</i> (2010)
Interleukin-8	Cytokine	Inflammation	LNCaP, 22Rv1	+	Indirect	Activation of NF κ B and AP-1	Seaton <i>et al.</i> (2008)
Endothelin-1	Hormone	Vasoconstrictor	LNCaP	+	Indirect	Activation of Myc	Lee <i>et al.</i> (2009)

(continued)

Table 1 Continued

Factor	Gene classification	Gene function	Cells	Effect	Direct or indirect	Supposed mechanism	References
HB-EGF	Growth factor	Mitogenic factor (ErbB1 agonist)	LNCaP	–	Indirect	Inhibition of AR transcription	Adam <i>et al.</i> (2002)
Activin A	Growth factor	TGF- β superfamily	LNCaP	+	Indirect	Activation of Smads	Kang <i>et al.</i> (2009)
Smad2, 3	Signal transduction	Cell proliferation, apoptosis, and differentiation	LNCaP	+	Direct	Activation of AR transcription	Kang <i>et al.</i> (2009)
Nemo-like kinase (NLK)	Kinase	MAPK-like kinase	LNCaP	–	Indirect	Inhibition of LEF1 and LEF1 complex	Emami <i>et al.</i> (2009)
ErbB3-binding protein 1 (EBP1)	RNA-binding protein	Growth regulation and differentiation	LNCaP	–	Direct	Inhibition of AR transactivation	Zhang <i>et al.</i> (2005)
Angiotensin II type 1	Hormone	Vasoconstrictor	LNCaP	+	Indirect	Activation of NF- κ B and c-myc	Hoshino <i>et al.</i> (2010)
AT1R	Receptor	Vasoconstrictor	LNCaP	+	Indirect	Activation of NF- κ B and c-myc	Hoshino <i>et al.</i> (2010)

+ / – , up/downregulation of androgen receptor.

transcriptional step is generally thought to play a critical role in gene expression. In addition, AR overexpression has been detected at both the protein and mRNA levels in CRPC, suggesting that transcriptional regulation of the *AR* gene is at least one of the major causes of AR dysregulation. In this review, we therefore summarize the factors involved in AR expression, with an emphasis on transcriptional regulation by transcription factors in PCa (Table 1). Furthermore, we also discuss the therapeutic potential of targeting AR expression for the treatment of PCa and CRPC, by considering the agents involved in the regulation of AR expression (Table 2).

Transcriptional regulation

Transcriptional control is thought to play a key role in the expression of a wide variety of genes, including *AR*. Transcription factors bind to DNA in a sequence-specific manner for each transcription factor, and positively or negatively affect gene expression through the control of transcription. The human *AR* is encoded by a single copy gene located on the X-chromosome. Two major mRNAs of 11 and 7.5 kb are transcribed from this gene, regulated by *cis*-acting elements in its promoter region. The human *AR* promoter region lacks a TATA-box and a CCAAT-box, and the binding sites for several transcription factors have been mapped (Tilley *et al.* 1990, Faber *et al.* 1991, 1993, Mizokami *et al.* 1994, Takane & McPhaul 1996). Several transcription factors have been reported to be responsible for controlling *AR* transcription. We discuss the relevance of these individual transcription factors in regulating AR expression, and in PCa.

cAMP response element-binding

cAMP response element-binding (CREB) is a transcription factor that binds to the cAMP response element (CRE, 5'-TGACGTGA-3'), thereby increasing or decreasing the transcription of its target genes. Several lines of evidence suggest that CREB is a proto-oncogene (Siu & Jin 2007).

Mizokami *et al.* (1994) isolated a 2.3-kb *AR* gene promoter region and analyzed it using a chloramphenicol acetyltransferase (CAT) assay. They found that the CRE was located between –530 and –380 bp from the transcription start site (TSS), and that *AR* transcription was increased by cAMP. They therefore suggested that the CREB transcription factor positively regulated *AR* transcription, although these results need to be confirmed using modern techniques.

The active form of phosphorylated CREB has been reported to be significantly increased in bone

Table 2 Agents involved in androgen receptor expression

Small molecule	Major function	Cells	Effect	Action level	Supposed mechanism	References
Natural compounds						
EGCG	Polyphenol	LNCaP	—	Transcription	Inhibition of Sp1	Ren <i>et al.</i> (2000)
Theaflavin-3,3'-digallate (TF3)	Polyphenol	LNCaP	—	Post-translational	Inhibition of rat liver microsomal 5 α -reductase activity	Lee <i>et al.</i> (2004)
Penta-O-galloyl- β -D-glucose (5GG)	Polyphenol	LNCaP	—	Post-translational	Inhibition of rat liver microsomal 5 α -reductase activity	Lee <i>et al.</i> (2004)
Quercetin	Polyphenol	LNCaP	—	Transcription	NA	Xing <i>et al.</i> (2001)
Quercetin	Polyphenol	LNCaP	—	Transcription	Activation of c-Jun	Yuan <i>et al.</i> (2004)
Resverol	Polyphenol	LNCaP	—	Transcription	Activation of c-Jun	Yuan <i>et al.</i> (2004)
Quercetin	Polyphenol	LNCaP	—	Transcription	Inhibition of Sp1	Yuan <i>et al.</i> (2005)
Genistein combined polysaccharide (GCP)	Polyphenol	LNCaP	—	Non-transcription	NA	Tepper <i>et al.</i> (2007)
Luteolin (3',4',5,7-tetrahydroxyflavone)	Polyphenol	LNCaP	—	transcription	NA	Chiu & Lin (2008)
Indole-3-carbinol	Compound found in vegetables	LNCaP	—	Transcription	NA	Hsu <i>et al.</i> (2005)
Phenethyl isothiocyanate (PEITC)	Compound found in vegetables	LNCaP	—	Transcription	Inhibition of Sp1	Wang <i>et al.</i> (2006)
D,L-sulforaphane (SFN)	Compound found in vegetables	LNCaP, C4-2	—	Transcription	NA	Su-Hyeong & Shivendra (2009)
Baicalin	Polyphenol (component of PC-SPES)	LNCaP	—	NA	NA	Chen <i>et al.</i> (2001)
Baicalin	Polyphenol (component of PC-SPES)	LNCaP	—	NA	NA	Chen <i>et al.</i> (2001)
Thymoquinone	Component of herbs	LNCaP, C4-2	—	NA	NA	Kaseb <i>et al.</i> (2007)
Gum mastic	Natural resin	LNCaP	—	Transcription	NA	He <i>et al.</i> (2006)
Acetyl-11-keto- β -boswellic acid (AKBA)	Natural resin	LNCaP	—	Transcription	Inhibition of Sp1	Yuan <i>et al.</i> (2008)
Selenium						
Methylselenocysteine (MSC)	Organic selenium-containing compounds	LNCaP	—	NA	NA	Lee <i>et al.</i> (2006)
Methylseleninic acid (MSA)	Organic selenium-containing compounds	LNCaP	—	Transcription	NA	Chun <i>et al.</i> (2006)
1,4-Phenylenebis(methylene)selenocyanate	Organic selenium-containing compounds	LNCaP, C4-2	—	NA	NA	Nicole <i>et al.</i> (2010)
Methylseleninic acid (MSeA)	Organic selenium-containing compounds	LNCaP, LAPC-4	—	Transcription	Inhibition of Sp1	Husbeck <i>et al.</i> (2006)
Selenite	Nonorganic selenium-containing compounds	LNCaP, LAPC-4	—	Transcription	Inhibition of Sp1	Husbeck <i>et al.</i> (2006)
Hormones and vitamins						
Androgen	Androgen	LNCaP	—	Transcription	NA	Brinkmann <i>et al.</i> (1989)
DHT	Androgen	LNCaP	+	Transcription	Activation of Myc	Lee <i>et al.</i> (2009)
R1881	Synthetic androgen	LNCaP	—	Transcription	NA	Ravenna <i>et al.</i> (1995)
Hydroxy-flutamide (OH-FLU)	Anti-androgen	LNCaP	—	Transcription	NA	Ravenna <i>et al.</i> (1995)
Fulvestrant (ICI 182 780)	Anti-estrogen	LNCaP	—	Transcription	NA	Bhattacharyya <i>et al.</i> (2006)
1,1-bis(3'-indolyl)-1-(p-substitutedphenyl) methanes (C-DIMs)	PPAR γ agonists	LNCaP	—	Transcription	PPAR γ -independent pathway	Chinthalapalli <i>et al.</i> (2007)
9-cis retinoic acid	Retinoic acid	LNCaP	+	Transcription	NA	Zhao <i>et al.</i> (1999)
1 α ,25-Dihydroxyvitamin D $_3$	Vitamin	LNCaP	+	Transcription	NA	Zhao <i>et al.</i> (1999)
α -Tocopheryl succinate (vitamin E succinate, VES)	Vitamin	LNCaP	—	Transcription	Inhibition of Sp1	Huang <i>et al.</i> (2009)
TS-1 (derivative of VES)	Vitamin	LNCaP	—	Transcription	Inhibition of Sp1	Huang <i>et al.</i> (2009)
Signal transduction						
cAMP	Signal transduction	LNCaP	+	Transcription	Activation of CREB	Mizokami <i>et al.</i> (1994)
A23187	Calcium ionophore	LNCaP	—	Transcription	Protein kinase C- or calmodulin-dependent pathways	Gong <i>et al.</i> (1995)

(continued)

Table 2 Continued

Small molecule	Major function	Cells	Effect	Action level	Supposed mechanism	References
Thapsigargin	Intracellular endoplasmic reticulum $\text{Ca}(2+)$ -ATPase inhibitor	LNCaP	—	Transcription	Protein kinase C- or calmodulin-dependent pathways	Gong <i>et al.</i> (1995)
Thapsigargin and its analogues	Intracellular endoplasmic reticulum $\text{Ca}(2+)$ -ATPase inhibitor	LNCaP, LAPC-4, VCaP, MDA-Pca-2b, 22Rv1	—	Translation	NA	Vander Griend <i>et al.</i> (2009)
Celecoxib	COX2 inhibitor	LNCaP	—	Transcription	Activation of c-Jun	Pan <i>et al.</i> (2003)
Nimesulide	COX2 inhibitor	LNCaP	—	Transcription	Activation of c-Jun	Pan <i>et al.</i> (2003)
Sulindac sulfide	Non-steroidal anti-inflammatory drug	LNCaP	—	Transcription	Activation of c-Jun, inhibition of Sp1, NF1 and CREB	Lim <i>et al.</i> (2003)
Sulindac sulfone (exisulind)	Non-steroidal anti-inflammatory drug	LNCaP	—	Transcription	Activation of c-Jun, inhibition of Sp1, NF1 and CREB	Lim <i>et al.</i> (2003)
CP248	Potent analogs of exisulind	LNCaP	—	Transcription	Activation of c-Jun, inhibition of Sp1, NF1 and CREB	Lim <i>et al.</i> (2003)
CP461	Potent analogs of exisulind	LNCaP	—	Transcription	Activation of c-Jun, inhibition of Sp1, NF1 and CREB	Lim <i>et al.</i> (2003)
Trichostatin A (TSA)	HDAC inhibitor	AI-LNCaP	—	Transcription	Restoring suppressor element (ARS)-binding complex	Wang <i>et al.</i> (2004)
Trichostatin A (TSA)	HDAC inhibitor	LNCaP	—	Transcription	NA	Rokhlin <i>et al.</i> (2006)
Suberohydroxamic acid	HDAC inhibitor	LNCaP	—	Transcription?	NA	Rokhlin <i>et al.</i> (2006)
Depsipeptide	HDAC inhibitor	LNCaP	—	Transcription?	NA	Rokhlin <i>et al.</i> (2006)
Sodium butyrate	HDAC inhibitor	LNCaP	—	Transcription?	NA	Rokhlin <i>et al.</i> (2006)
Sodium butyrate	HDAC inhibitor	LNCaP	+	NA	NA	Kim <i>et al.</i> (2007)
Suberoylanilide hydroxamic acid (SAHA, vorinostat)	HDAC inhibitor	LNCaP	—	Transcription	NA	Marrocco <i>et al.</i> (2007)
Parthenolide	NF- κ B inhibitor	LNCaP, 22Rv1	—	Transcription	Inhibition of NF- κ B	Zhang <i>et al.</i> (2009)
AZ10397767 ^a	CXC-chemokine receptor-2 inhibitor	LNCaP	—	Transcription	Inhibition of IL8 receptor	Seaton <i>et al.</i> (2008)
BAY11-7082 ^a	NF- κ B inhibitor	LNCaP	—	Transcription	Inhibition of NF- κ B induced by IL8	Seaton <i>et al.</i> (2008)
JNK inhibitor I ^a	JNK inhibitor	LNCaP	—	Transcription	Inhibition of AP-1	Seaton <i>et al.</i> (2008)
Others						
Doxorubicin	Anticancer drug (anthracycline)	LNCaP	—	NA	NA	Rokhlin <i>et al.</i> (2006)
Etoposide	Anticancer drug (topoisomerase II inhibitor)	LNCaP	—	Transcription	NA	Liu & Yamauchi (2010)
Anti- β 2-microglobulin polyclonal antibody	Antibody	LNCaP, C4-2	—	Transcription	NA	Huang <i>et al.</i> (2008)
Anti- β 2-microglobulin monoclonal antibody	Antibody	LNCaP, C4-2	—	Transcription	Inhibition of SREBP-1	Huang <i>et al.</i> (2010)
Resveratrol	Phytoalexin	LNCaP	—	Transcription	NA	Mitchell <i>et al.</i> (1999)
Nigerican	Antibiotic	LNCaP, 22Rv1	—	Transcription	NA	Mashima <i>et al.</i> (2010)
Clioquinol (CQ)	Therapeutic agent for Alzheimer's disease	LNCaP, C4-2	—	NA	NA	Chen <i>et al.</i> (2007)
Dibenzoylmethane	β 3-Diketone	LNCaP	—	Transcription	NA	Jackson <i>et al.</i> (2007)
Functional domain of saposin C	Neurotrophic peptide	LNCaP	+	Transcription	NA	Ding <i>et al.</i> (2007)
3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole	Triazole derivative	LNCaP	—	Transcription	NA	Loiarro <i>et al.</i> (2011)

NA, not available.

^aWhen IL8 was added to serum-free media; +/–, up/downregulation of androgen receptor.

metastatic PCa. In addition, a PCa progression model demonstrating epithelial–mesenchymal transition (EMT) also showed an increase of CREB phosphorylation associated with progression (Wu *et al.* 2007), and CREB-regulated transcription has recently been reported to induce neuroendocrine-like differentiation (Deng *et al.* 2008). Thus, CREB may promote the pathogenesis of PCa through controlling the expression of AR and other target genes.

Myc

The *Myc* gene, located on chromosome 8, encodes a transcription factor that regulates the expression of its target genes by binding to an enhancer sequence (E-box, 5'-CAC(A/G)TG-3') (Adhikary & Eilers 2005). Mutated *Myc* genes that are persistently expressed are found in many cancers, resulting in the aberrant expression of many genes involved in cell proliferation, and subsequent cancer formation; t(8;14) is a common translocation that is involved in the development of Burkitt's lymphoma (Boxer & Dang 2001). In contrast, numerous studies have demonstrated that inhibition of Myc leads to growth retardation and cell death in many cancers, making it a potential target for anti-cancer drugs (Hermeking 2003).

Myc has been found to be involved in *AR* transcriptional expression. Using a reporter gene assay in *AR*-nonexpressing PC-3 cells, Grad *et al.* (1999) showed that Myc positively regulated *AR* transcription by binding to the E-box region. This finding was supported by the results of a study indicating that the introduction of a mutation into the E-box in the *AR* promoter region decreased its transcription, as measured by CAT assay (Takane & McPhaul 1996). Recently, in a more definitive manner, Myc was proven to regulate *AR* transcription in LNCaP cells that express *AR*, and are the standard cell line used as a model for androgen-dependent PCa (Lee *et al.* 2009).

Myc is a well-known proto-oncogene, and many associations between Myc and oncogenesis have been reported in PCa. Elevated Myc expression in primary prostate tumors was recently reported to be a predictor of biochemical recurrence after radical prostatectomy (Hawsworth *et al.* 2010), which is consistent with the finding that higher *AR* expression is a predictor of poor outcome in patients treated with radical prostatectomy (Li *et al.* 2004, Rosner *et al.* 2007). Similarly, a recent study found that increased *Myc* gene copy number correlated with higher Gleason score (Chen *et al.* 2010), while Myc overexpression reduced the expression of the tumor-suppressor gene *Nkx3.1* and induced prostate cellular transformation in a mouse model (Iwata *et al.* 2010).

c-Jun

c-Jun is a member of the activator protein-1 (AP-1) transcription complex, which is a heterodimeric protein composed of proteins belonging to the c-Fos, c-Jun, ATF, and JDP families. AP-1 upregulates the transcription of genes containing the tetradecanoyl-phorbol 13-acetate-responsive element (TRE; 5'-TGA(G/C)TCA-3') (Hess *et al.* 2004), and regulates gene expression in response to a variety of stimuli, including cytokines, growth factors, stresses, and infections (Hess *et al.* 2004). AP-1 in turn controls a number of cellular processes, including differentiation, proliferation, and apoptosis (Ameyar *et al.* 2003).

c-Jun was reported to suppress *AR* transcription in a reporter gene assay using the *AR* promoter region in LNCaP cells (Pan *et al.* 2003). Similarly, the same group used a gel-shift assay to show that c-Jun bound to the TRE in the *AR* promoter region and repressed *AR* transcription (Yuan *et al.* 2004).

Although c-Jun is known to suppress *AR* expression, it also functions as an *AR* coactivator (Bubulya *et al.* 2000, Chen *et al.* 2006). Consistent with this notion, c-Jun is highly expressed in PCa tissues, compared with benign prostate hypertrophy tissues (Tiniakos *et al.* 2006). Similarly, patients with high expression levels of the active form of phosphorylated c-Jun had significantly shorter relapse-free survival times, compared with patients with low phosphorylated c-Jun protein expression, suggesting that increased active-c-Jun levels may promote castration-resistant tumor growth (Edwards *et al.* 2004). c-Jun suppression using antisense RNA strongly compromised the androgen-dependent proliferation of LNCaP cells (Chen *et al.* 2006). Overall, these findings suggest that c-Jun may be more involved in promoting *AR* function than in suppressing *AR* expression.

Sp1

Sp1 is a member of the Sp/KLF family of transcription factors that is involved in early development. Sp1 contains a zinc-finger protein motif, by which it binds directly to the consensus sequence 5'-(G/T)GGGCGG (G/A)(G/A)(C/T)-3' (GC-box) and enhances gene transcription (Black *et al.* 2001).

In 1993, Faber *et al.* characterized the *AR* promoter region and identified a short GC-box (−59/−32 bp from TSS) and a long homopurine stretch (−117/−60 bp from TSS). They also implicated Sp1 in the control of *AR* transcription using a gene reporter assay and footprint analysis (Faber *et al.* 1993). These results were supported by a study demonstrating that the introduction of a mutation into the GC-box in the *AR* promoter region decreased *AR* transcription, as measured by CAT assay (Takane & McPhaul 1996).

This finding was recently confirmed using LNCaP cells, showing that Sp1 overexpression increased *AR* transcription (Yuan *et al.* 2005). However, although a relationship between Sp1 and AR has been demonstrated, to the best of our knowledge, there have been no reports concerning the role of Sp1 in PCa.

p53

p53 is encoded by the *TP53* gene, and is a tumor suppressor protein and transcription factor that binds to the p53-specific sequence (5'-(A/G)(A/G)(A/G)-C(A/T)(T/A)G(T/C)(T/C)(T/C)-3' (Matlashewski *et al.* 1984, Isobe *et al.* 1986, McBride *et al.* 1986, Kern *et al.* 1991). p53 is important in multicellular organisms, where it regulates the cell cycle, cellular apoptosis, and DNA repair, and functions as a tumor suppressor. As such, p53 has been described as 'the guardian of the genome', referring to its role in preventing genome mutation.

Forced p53 expression in LNCaP cells reduced *AR* transcription, while conversely, p53 knockdown increased *AR* transcription by binding to the p53 DNA-binding consensus sequence in the *AR* promoter region (−488/−469 bp from TSS; Alimirah *et al.* 2007).

Numerous studies concerning p53 have been performed in PCa and other solid cancers, and have suggested that mutations in the *TP53* gene are associated with PCa progression (Navone *et al.* 1993, Bauer *et al.* 1995, Heidenberg *et al.* 1995, Nesslinger *et al.* 2003). Moreover, *TP53* mutations may be an indicator of poor prognosis in PCa (Bauer *et al.* 1995, Heidenberg *et al.* 1995). Consistent with the above observations, it is interesting to note that the majority of metastatic PCa-derived cell lines harbor *TP53* and/or *AR* mutations (Sobel & Sadar 2005). These observations suggest an important functional relationship between p53 and AR in the progression of PCa.

Foxo3a

Foxo3a belongs to the subclass 'O' of the forkhead family of transcription factors. These are characterized by a distinct forkhead DNA-binding domain, and bind to the Foxo-response element (5'-TTGTTTAC-3') (Durham *et al.* 1999, Furuyama *et al.* 2000). There are three other human Foxo family members: Foxo1, Foxo4, and Foxo6. Foxo3a likely functions as a trigger for apoptosis through upregulation of pro-apoptotic proteins such as Bim and PUMA (Ekoff *et al.* 2007), or the downregulation of anti-apoptotic proteins such as FLIP (Skurk *et al.* 2004). Deregulation of Foxo3a is involved in tumorigenesis; for example, translocation of this gene with the *MLL* gene is associated with

secondary acute leukemia (Myatt & Lam 2007), and Foxo3a is thus known as a tumor suppressor.

Chang and colleagues reported that Foxo3a positively regulated *AR* transcription by binding to the Foxo-response element in the *AR* promoter region (−1297/−1290 bp from TSS), and demonstrated a preventative role for the AR in the apoptosis of LNCaP cells by inhibition of the phosphoinositide 3-kinase/Akt signaling pathway (Yang *et al.* 2005).

The Foxo3a protein is the most highly expressed Foxo family member in PCa cells. It is hyperphosphorylated and markedly reduced in CRPC cells compared with androgen-dependent PCa cells (Lynch *et al.* 2005). Thus, Foxo function is compromised in CRPC cells, which appears to be incompatible with the observation that AR is frequently overexpressed in CRPC, but is consistent with its function in promoting apoptosis.

Lymphoid enhancer-binding factor 1

Lymphoid enhancer-binding factor 1 (LEF1) is the nuclear transducer of the activated-Wnt pathway. It binds to the LEF/TCF-binding site, 5'-(A/T)(A/T)CAAG-3', and regulates the expression of its target genes (Roose & Clevers 1999). The Wnt-1/β-catenin/LEF1 pathway has been implicated in *AR* transcription, and Wnt-1 signaling leads to activation of the LEF1 complex and increased *AR* transcription (Yang *et al.* 2006). Moreover, LEF1 also positively regulates *AR* transcription by binding directly to LEF/TCF-binding sites (between −2000 and +0 bp from TSS), and was shown by microarray analysis to be upregulated in CRPC cells (Li *et al.* 2009).

Many studies have indicated a functional link between Wnt signaling and PCa (Yardy & Brewster 2005, Verras & Sun 2006), and intriguingly, a specific protein–protein interaction between β-catenin and AR resulting in AR transactivation has been demonstrated (Yang *et al.* 2002). Levels of both Wnt-1 and β-catenin were low in normal prostate cells, but were highly expressed in PCa cells. Increased Wnt-1 and β-catenin expression levels were also directly related to the Gleason score and to serum prostate-specific antigen (PSA) levels in PCa patients (Chen *et al.* 2004a,b). In addition, many studies have reported abnormal expression and mutation of β-catenin in PCa and in other solid cancers (Yardy & Brewster 2005). Synchronous activation of K-ras and β-catenin significantly reduced survival in a mouse model, associated with accelerated tumorigenesis and the development of invasive carcinoma (Pearson *et al.* 2009). In addition, Wnt/β-catenin activation promoted PCa progression in another mouse model (Yu *et al.* 2010), and the small molecule inhibitor of Wnt/β-catenin signaling,

PKF118–310, has recently been shown to inhibit the proliferation of PCa cells (Lu *et al.* 2009).

Purine-rich element-binding protein α

Purine-rich element-binding protein α (PUR α) is a nuclear protein with the ability to specifically bind to a purine-rich element found in single-stranded DNA (Bergemann & Johnson 1992, Bergemann *et al.* 1992). PUR α binds to both DNA and RNA, and is believed to be involved in diverse functions, including DNA replication, gene transcription, mRNA translation, and RNA transport (Gallia *et al.* 2000). Several studies have indicated a role for PUR α in the regulation of cell growth (Chang *et al.* 1996, Itoh *et al.* 1998, Stacey *et al.* 1999, Gallia *et al.* 2000, Barr & Johnson 2001, Darbinian *et al.* 2001, Lezon-Geyda *et al.* 2001).

Ferrari's group reported that AR transcription was inhibited by a novel transcriptional complex containing PUR α and heterogeneous nuclear ribonucleoprotein-K (hnRNP-K), through binding to a specific sequence (repressor element) in the AR gene 5'-untranslated region. Furthermore, PUR α expression was decreased in CRPC cells and tissues, implicating it in the pathogenesis of CRPC (Wang *et al.* 2008).

PUR α expression is attenuated in CRPC cells compared with androgen-dependent PCa cells (Inoue *et al.* 2008). Recent studies demonstrated that overexpression of PUR α in PC-3 and DU145 cells repressed their proliferation *in vitro* (Wang *et al.* 2008). Intriguingly, PUR α has been shown to interact with several cellular regulatory proteins, including the E2F-1 and hypophosphorylated form of retinoblastoma protein (pRb; Johnson *et al.* 1995, Darbinian *et al.* 1999), both of which have been implicated in PCa progression (Yeh *et al.* 1998, Davis *et al.* 2006).

NF κ B

NF κ B (p65) is a protein complex that controls the transcription of various target genes, and is involved in cellular responses to stimuli such as stresses, cytokines, and infections (Gilmore 1999, 2006, Tian & Brasier 2003, Brasier 2006, Perkins 2007). NF κ B regulates the expression of genes controlling cell proliferation and survival. Aberrant activation of NF κ B is frequently seen in many cancers, and induces the expression of genes promoting cell proliferation and protecting against apoptosis. Conversely, defects in NF κ B result in suppression of cell growth and increased susceptibility to apoptosis, leading to increased cell death. NF κ B inhibition can suppress tumor growth, induce apoptosis, and sensitize cells to anti-cancer agents in various cancers.

NF κ B was recently found to positively regulate AR transcription and cell growth in PCa cells (Zhang *et al.* 2009), though it was previously shown to act as a negative regulator of AR transcription in rat hepatic cells (Supakar *et al.* 1995). Furthermore, the inhibitor of NF κ B has shown antitumor activity, even in CRPC cells. The results of another study using rat Sertoli cells support the positive regulation of AR expression by NF κ B (Zhang *et al.* 2004).

Several studies have examined the expression of NF κ B in PCa, and its relationship to clinical features. NF κ B was overexpressed in prostatic intraepithelial neoplasia and PCa compared with benign epithelium (Sweeney *et al.* 2004), and recent studies found that NF κ B expression was predictive of biochemical recurrence in patients with positive surgical margins after radical prostatectomy (Ismail *et al.* 2004). Nuclear localization of NF κ B is increased in PCa with lymph node metastasis (Ismail *et al.* 2004), and can be used to predict patient outcome (Lessard *et al.* 2003). These results suggest that NF κ B is frequently activated in PCa, and that its expression may be related to progression. NF κ B is constitutively activated in CRPC xenografts where AR expression is also upregulated, suggesting a positive correlation between NF κ B and AR expression (Chen & Sawyers 2002, Chen *et al.* 2004a,b).

Twist1

Twist1 belongs to the family of basic helix–loop–helix transcription factors that binds to the E-box sequence (5'-CANNTG-3'), and has been proposed to be an oncogene (Olson & Klein 1994, Maestro *et al.* 1999). Gene profiling analyses revealed that upregulation of Twist1 was associated with malignant transformation (van Doorn *et al.* 2004, Hoek *et al.* 2004). In addition, increased Twist1 expression has been detected in various malignant tumors compared with its expression in nonmalignant tissues (Maestro *et al.* 1999, Rosivatz *et al.* 2002), and was correlated with poorer outcome and shorter survival (Hoek *et al.* 2004). Recent evidence has also implicated Twist1 as a key factor responsible for metastasis (Yang *et al.* 2004).

We recently showed that Twist positively regulated AR expression in response to oxidative stress induced by androgen deprivation (Shiota *et al.* 2010). This finding is also supported by the study, similar to Myc (Takane & McPhaul 1996). Twist1 is a well-known master regulator of EMT, which may indicate a functional link between EMT and androgen/AR signaling.

Twist1 was upregulated in PCa with high Gleason score, and was involved in its colony forming and invasive abilities (Kwok *et al.* 2005). In another report, nuclear Twist expression was an important predictive factor for the metastatic potential of primary PCa (Yuen *et al.* 2007).

E2F/Rb

The E2F family of transcription factors consists of nine members, all of which bind to the E2F-binding site (5'-TTTCGCGC-3') in the target promoter sequence. Three of them are activators: E2F-1, E2F-2, and E2F-3a, while the remaining six, E2F-3b and E2F-4–8, act as suppressors. The tumor suppressor protein pRb binds to E2F-1, and thus prevents its transcription-promoting activity. In the absence of pRb, E2F-1 transactivates its target genes, which facilitate the G1/S transition phase and S-phase (Pardee *et al.* 2004).

E2F-1 was shown to negatively regulate *AR* transcription in LNCaP cells (Davis *et al.* 2006). In this study, E2F-1 expression was elevated during prostate carcinogenesis and PCa progression, while AR expression was decreased in metastatic tissues from CRPC, in contrast to the results of many previous studies. Paradoxically, Knudsen's group recently reported that pRb knock-down with E2F-1 and E2F-3a overexpression cooperatively upregulated *AR* transcription in LNCaP cells (Sharma *et al.* 2010). In clinical samples, pRb and E2F-1 expression were negatively and positively correlated with AR expression, respectively. Furthermore, pRb expression in clinical samples was inversely correlated with the transition to CRPC.

Rb mutations have been linked to the development of PCa, and loss of heterozygosity of the *Rb* locus has been observed in clinical PCa samples (Ittmann & Wiczorek 1996). In a mouse model, pRb inactivation promoted prostate carcinogenesis and PCa progression (Maddison *et al.* 2004, Zhou *et al.* 2006). Intriguingly, fluorescence *in situ* hybridization analysis revealed that loss of the *Rb* gene was nearly four times more common after ADT than before therapy (22 vs 6%; Kaltz-Wittmer *et al.* 2000).

Sterol regulatory element-binding protein-1

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that bind to the sterol regulatory element (5'-TCACNCCAC-3'). Mammalian SREBPs consist of SREBP-1 and SREBP-2, encoded by *SREBF-1* and *SREBF-2*, respectively. SREBPs belong to the basic helix–loop–helix leucine zipper class of transcription factors (Yokoyama *et al.* 1993). Inactivated SREBPs are attached to the nuclear envelope and endoplasmic reticulum membranes. Decreased levels of sterols are associated with cleavage of SREBPs and translocation of the N-terminal domain to the nucleus. These activated SREBPs then bind to a specific sterol regulatory element, thus upregulating the synthesis of enzymes involved in sterol biosynthesis (Gasic 1994, Wang *et al.* 1994). Sterols in turn inhibit the cleavage of SREBPs, thus reducing the synthesis of additional sterols via negative feedback.

SREBP-1 was recently found to positively regulate *AR* transcription in LNCaP cells. SREBP-1 binding to the sterol regulatory element (–347/–336 bp from TSS) was demonstrated by gel-shift assay and chromatin-immunoprecipitation assay, while the regulation of *AR* transcription by SREBP-1 was proven by gene reporter assay using the *AR* promoter region (Huang *et al.* 2010).

SREBPs and their downstream effector genes have been found to be upregulated during progression to CRPC in the LNCaP xenograft model, as well as in clinical specimens of PCa (Ettinger *et al.* 2004). Intriguingly, 5- α reductase type 2 was also regulated by SREBPs in mouse prostate (Seo *et al.* 2009), and androgens and AR were found to reciprocally mediate SREBP-1 expression in PCa cells (Heemers *et al.* 2006, Ngan *et al.* 2009). This mutual regulation of SREBPs and androgen/AR signaling suggests a relationship between lipogenesis and PCa. In addition, pharmacologic inhibition of lipogenesis or RNA interference-mediated downregulation of key lipogenic genes induced apoptosis in cancer cell lines and reduced tumor growth in xenograft models. Lipogenesis is already seen in the earliest stages of prostate carcinogenesis, and increases with the development of CRPC (Swinnen *et al.* 2004).

Other factors

In addition to the transcription factors themselves, other molecules related to extracellular and intracellular signal transduction have also been implicated in *AR* transcription, through their regulation of known or unknown transcription factors (Table 1). Several of these factors have been reported to be involved in prostate carcinogenesis and PCa progression.

Clinical implications of targeting AR expression in PCa

As noted above, AR expression is regulated at the transcriptional level by several transcription factors, and various transcription factors are upregulated in PCa and CRPC, implicating them in the pathogenesis of these conditions. Suppression of AR expression is known to induce tumor regression in PCa, and even in CRPC (Chen *et al.* 2004a,b), and a strategy targeting AR expression may therefore be applicable to the treatment of PCa and CRPC. Indeed, the suppression of factors regulating AR expression using various methods, including RNA interference-mediated knock-down, small molecules, and antibodies, suppressed cell growth. The agents affecting *AR* transcription are listed in Table 2. In this list, a few inconsistencies among the reports were found. First, in androgen and synthetic

androgen, R1881 had suppressive effect on AR expression at transcriptional level whereas Lee *et al.* reported dihydrotestosterone upregulated AR transcriptional level. Secondly, various histone deacetylase (HDAC) inhibitors downregulated AR expression in LNCaP cells although only Kim *et al.* (2007) reported that sodium butyrate upregulated AR expression. Although these inconsistencies might be derived from the differences of experimental condition, our data supported the result that androgen including dihydrotestosterone suppressed AR transcript (data not shown). Thus, androgen suppressed AR transcript whereas androgen is known to increase AR protein level by enhancing stability of AR protein (Gregory *et al.* 2001). This fact indicates that androgen functions not only as a ligand of the AR, but also as an AR stabilizer. Thus, androgen coordinately activates genomic and non-genomic AR downstream signaling.

These agents listed in Table 2 can be classified into several categories, according to their functions, and their therapeutic potentials are discussed below.

HDAC inhibitors have been intensively investigated as AR suppressors. Various HDAC inhibitors suppressed AR expression in LNCaP cells, supposedly at the transcriptional level, consistent with the results of many studies showing that HDAC inhibitors inhibited cell growth in PCa, and that HDAC was closely implicated in PCa progression (Abbas & Gupta 2008). So far, several HDAC inhibitors have been shown to exert anticancer effects in PCa using *in vitro* and *in vivo* models (Butler *et al.* 2000, Kuefer *et al.* 2004, Rephaeli *et al.* 2005, Kulp *et al.* 2006, Shabbeer *et al.* 2007, Sargeant *et al.* 2008, Hwang *et al.* 2010). Recently, a phase II trial using a HDAC inhibitor romidepsin was conducted in chemo-naïve patients with progressing and metastatic CRPC. However, the result was rather disappointing (Molife *et al.* 2010). Similarly, a phase II trial using another HDAC inhibitor vorinostat in advanced PCa patients progressing on prior chemotherapy showed an unsatisfactory result (Bradley *et al.* 2009). Also, the HDAC inhibitor, panobinostat, in CRPC patients exerted no remarkable efficiency in a phase I trial (Rathkopf *et al.* 2010). Thus, HDAC inhibitors seem to be less promising, at least in the treatment of CRPC.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been available for many years and are widely used throughout the world. NSAIDs have also been proved to suppress AR transcription through modulation of transcription factors responsible for AR expression. Several preclinical studies have shown that NSAIDs inhibited PCa proliferation and induced cellular apoptosis *in vitro* and *in vivo* (Goluboff *et al.* 1999, Lim *et al.* 2003, Patel *et al.* 2005, Shigemura *et al.* 2005). Furthermore, several clinical trials have proven the efficiency of NSAIDs for the treatment of PCa. In a pilot study, the COX-2 inhibitor, celecoxib, reduced

the rate of elevation of PSA after biochemical recurrence following radical prostatectomy and radiation therapy (Pruthi *et al.* 2004). This finding was proven by the following phase II trial (Pruthi *et al.* 2006). Similarly, sulindac sulfone (exisulind), a metabolite of the NSAID sulindac, also exerted a favorable effect on PSA recurrence after radical prostatectomy (Goluboff *et al.* 2001).

Selenium-containing compounds have also been extensively examined and have been found to suppress AR expression, probably at the transcriptional level. *In vitro* studies using androgen-dependent LNCaP and androgen-independent PC-3 cells have revealed that selenium could inhibit cell proliferation and induce apoptosis (Dong *et al.* 2003, Zhao *et al.* 2004). Also, in *in vivo* studies, selenium suppressed AR expression and growth of human PCa xenografts (Lee *et al.* 2006, Bhattacharyya *et al.* 2008). These findings are compatible with the results of a large-scale trial (Nutritional Prevention of Cancer (NPC) Trial; the Selenium and Vitamin E Chemoprevention Trial, SELECT), which indicated that selenium supplementation could reduce prostate carcinogenesis (Duffield-Lillico *et al.* 2003, Lippman *et al.* 2005). Because inorganic selenium compounds are known to produce genotoxic effects, organic selenium-containing compounds, which are better tolerated and exhibit anti-carcinogenic activity, seem to be more suitable for clinical usage.

Natural compounds, including polyphenols and natural resins, have also been investigated and found to reduce AR expression at both the transcriptional and post-transcriptional levels, with supposed tumor-suppressor roles in PCa. Many preclinical studies showed that various natural compounds exerted suppressive effects on PCa growth *in vitro* and *in vivo*. In addition, a phase II trial was conducted using phytochemicals in pomegranate juice for patients with recurrence after surgery or radiation for PCa, which showed that the PSA elevation rate was mitigated (Pantuck *et al.* 2006). Moreover, several chemicals that inhibit signaling pathways have also been reported, and show similar results to direct inhibition of their target molecules.

These and other agents under development that target AR expression have potential as chemopreventive compounds and therapeutic agents for PCa. Targeting AR expression at the transcriptional level, rather than directly targeting the AR itself through the use, e.g., of anti-androgens has several advantages. First, compounds targeting AR expression may exert additional effects on other targets implicated in tumor progression and suppression; indeed, some of the agents listed in Table 2 could affect the expression of various genes, such as cyclins and E2F, and signaling pathways, such as the Akt and mitogen-activated protein kinase pathways. Secondly, this strategy may be

applicable to AR splice variants that are potentially refractory to anti-androgens, which bind to the ligand-binding domain of the AR, because splice variants may lack the ligand-binding domain and are thus active in the absence of ligand binding.

Conclusions and future directions

AR is known to contribute to prostate tumorigenesis and progression, as well as to the development of CRPC. This is supported by substantial evidence implicating the aberrant expression or improper regulation of AR in these disorders. Several factors, including transcription factors, regulate AR expression, and offer a feasible strategy for developing new therapeutic agents to treat both androgen-dependent PCa and CRPC. Recent research into AR splice variants has revealed the importance of developing AR-expression-targeting therapeutics able to regulate the expression of AR splice variants.

Further *in vitro* and *in vivo* studies, together with intelligently designed clinical trials, are needed to evaluate compounds suppressing AR expression for treatment of PCa and CRPC. Moreover, based on the findings obtained so far, novel therapeutic strategies and agents for treatment of PCa and CRPC through disruption of AR expression should be developed.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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