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 at 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.

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, Zegarra-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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Gene classification</th>
<th>Gene function</th>
<th>Cells</th>
<th>Effect</th>
<th>Direct or Indirect</th>
<th>Supposed mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREB</td>
<td>Transcription factor</td>
<td>Induction of genes in response to hormonal stimulation of the cAMP pathway</td>
<td>LNCaP</td>
<td>+</td>
<td>Direct</td>
<td>Binding to CRE site</td>
<td>Mizokami et al. (1994)</td>
</tr>
<tr>
<td>Myc</td>
<td>Transcription factor</td>
<td>Cell cycle progression, apoptosis, and cellular transformation</td>
<td>Vitro</td>
<td>+</td>
<td>Direct</td>
<td>Binding to E-box</td>
<td>Grad et al. (1999)</td>
</tr>
<tr>
<td>Myc</td>
<td>Transcription factor</td>
<td>Cell cycle progression, apoptosis, and cellular transformation</td>
<td>LNCaP</td>
<td>+</td>
<td>Indirect</td>
<td>Binding to E-box</td>
<td>Lee et al. (2009)</td>
</tr>
<tr>
<td>c-Jun</td>
<td>Transcription factor</td>
<td>Transforming gene</td>
<td>LNCaP</td>
<td>–</td>
<td>Direct</td>
<td>Binding to TRE site</td>
<td>Pan et al. (2003)</td>
</tr>
<tr>
<td>c-Jun</td>
<td>Transcription factor</td>
<td>Transforming gene</td>
<td>LNCaP</td>
<td>–</td>
<td>Direct</td>
<td>Binding to TRE site</td>
<td>Yuan et al. (2004)</td>
</tr>
<tr>
<td>Sp1</td>
<td>Transcription factor</td>
<td>Constitutive induction of genes</td>
<td>Vitro</td>
<td>+</td>
<td>Direct</td>
<td>Binding to GC-box</td>
<td>Faber et al. (1993)</td>
</tr>
<tr>
<td>Sp1</td>
<td>Transcription factor</td>
<td>Constitutive induction of genes</td>
<td>LNCaP</td>
<td>+</td>
<td>Direct</td>
<td>Binding to GC-box</td>
<td>Yuan et al. (2005)</td>
</tr>
<tr>
<td>p53</td>
<td>Transcription factor</td>
<td>Cell cycle arrest, apoptosis, senescence, DNA repair, and metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Almirah et al. (2007)</td>
</tr>
<tr>
<td>Foxo3a</td>
<td>Transcription factor</td>
<td>Trigger for apoptosis</td>
<td>LNCaP</td>
<td>+</td>
<td>Direct</td>
<td>Binding to Foxo-response element</td>
<td>Yang et al. (2005)</td>
</tr>
<tr>
<td>LEF1</td>
<td>Transcription factor</td>
<td>Hair cell differentiation, follicle morphogenesis, and cellular transformation</td>
<td>LNCaP</td>
<td>+</td>
<td>Direct</td>
<td>Binding to LEF/TCF-binding site</td>
<td>Yang et al. (2006)</td>
</tr>
<tr>
<td>LEF1</td>
<td>Transcription factor</td>
<td>Hair cell differentiation, follicle morphogenesis, and cellular transformation</td>
<td>LNCaP, Al-LNCaP</td>
<td>+</td>
<td>Direct</td>
<td>Binding to LEF/TCF-binding site</td>
<td>Li et al. (2009)</td>
</tr>
<tr>
<td>Wnt-1</td>
<td>Oxytocin</td>
<td>Oncogenesis and developmental processes</td>
<td>LNCaP</td>
<td>+</td>
<td>Indirect</td>
<td>Activation of β-catenin</td>
<td>Yang et al. (2006)</td>
</tr>
<tr>
<td>β-Catenin</td>
<td>Signal transduction</td>
<td>Cell growth and adhesion</td>
<td>LNCaP</td>
<td>+</td>
<td>Direct</td>
<td>Activation of LEF1 and LEF1 complex</td>
<td>Yang et al. (2006)</td>
</tr>
<tr>
<td>Purz</td>
<td>Transcription factor</td>
<td>DNA replication and transcription</td>
<td>LNCaP</td>
<td>–</td>
<td>Direct</td>
<td>Binding to suppressor element (ARS) binding sites</td>
<td>Wang et al. (2008)</td>
</tr>
<tr>
<td>NFκB</td>
<td>Transcription factor</td>
<td>Cellular transformation and inflammation</td>
<td>LNCaP</td>
<td>–</td>
<td>Direct</td>
<td>Binding to NFκB-binding site</td>
<td>Zhang et al. (2009)</td>
</tr>
<tr>
<td>Twist1</td>
<td>Transcription factor</td>
<td>Differentiation, epithelial–mesenchymal transition</td>
<td>LNCaP, 22Rv1, CxR</td>
<td>+</td>
<td>Direct</td>
<td>Binding to E-box</td>
<td>Shiota et al. (2010)</td>
</tr>
<tr>
<td>E2F1</td>
<td>Transcription factor</td>
<td>Cell cycle progression</td>
<td>LNCaP</td>
<td>–</td>
<td>Direct</td>
<td>Binding to E2F-binding site</td>
<td>Davis et al. (2006)</td>
</tr>
<tr>
<td>E2F1, E2F3</td>
<td>Transcription factor</td>
<td>Cell cycle progression</td>
<td>LNCaP</td>
<td>+</td>
<td>Direct</td>
<td>Binding to E2F-binding site</td>
<td>Sharma et al. (2010)</td>
</tr>
<tr>
<td>Rb1</td>
<td>Transcription cofactor</td>
<td>Cell cycle arrest and tumor suppressor</td>
<td>LNCaP, LAPC-4</td>
<td>–</td>
<td>Direct</td>
<td>Inhibition of E2F1 transactivation</td>
<td>Sharma et al. (2010)</td>
</tr>
<tr>
<td>SREBP-1</td>
<td>Transcription factor</td>
<td>Sterol biosynthesis</td>
<td>LNCaP, C4-2</td>
<td>+</td>
<td>Direct</td>
<td>Binding to sterol regulatory element</td>
<td>Huang et al. (2010)</td>
</tr>
<tr>
<td>β2-Microglobulin</td>
<td>Membrane protein</td>
<td>Endocytosis of iron</td>
<td>LNCaP, C4-2</td>
<td>+</td>
<td>Indirect</td>
<td>Activation of SREBP-1</td>
<td>Huang et al. (2010)</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>Cytokine</td>
<td>Inflammation</td>
<td>LNCaP, 22Rv1</td>
<td>+</td>
<td>Indirect</td>
<td>Activation of NFκB and AP-1</td>
<td>Seaton et al. (2008)</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Hormone</td>
<td>Vasoconstrictor</td>
<td>LNCaP</td>
<td>+</td>
<td>Indirect</td>
<td>Activation of Myc</td>
<td>Lee et al. (2009)</td>
</tr>
</tbody>
</table>

(continued)
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 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).
<table>
<thead>
<tr>
<th>Small molecule</th>
<th>Major function</th>
<th>Action level</th>
<th>Action</th>
<th>Supposed mechanism</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural compounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGCG</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>Inhibition of Sp1</td>
<td>Ren et al. (2000)</td>
</tr>
<tr>
<td>Theaflavin-3,3′-digallate (TF3)</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Post-translational</td>
<td>Inhibition of rat liver microsomal 5α-reductase activity</td>
<td>Lee et al. (2004)</td>
</tr>
<tr>
<td>Penta-O-galloyl-b-D-glucose (5GG)</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Post-translational</td>
<td>Inhibition of rat liver microsomal 5α-reductase activity</td>
<td>Lee et al. (2004)</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Xing et al. (2001)</td>
</tr>
<tr>
<td>Resverol</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>Activation of c-Jun</td>
<td>Yuan et al. (2004)</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>Inhibition of Sp1</td>
<td>Yuan et al. (2005)</td>
</tr>
<tr>
<td>Genistein combined polysaccharide (GCP)</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Non-transcription</td>
<td>NA</td>
<td>Tepper et al. (2007)</td>
</tr>
<tr>
<td>Leteolin (3,4,5,7-tetrahydroxyflavone)</td>
<td>Polyphenol</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Chiu &amp; Lin (2008)</td>
</tr>
<tr>
<td>Indole-3-carbinol</td>
<td>Compound found in vegetables</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Hsu et al. (2005)</td>
</tr>
<tr>
<td>Phenethyl isothiocyanate (PEITC)</td>
<td>Compound found in vegetables</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>Inhibition of Sp1</td>
<td>Wang et al. (2006)</td>
</tr>
<tr>
<td>D,L-sulforaphane (SFN)</td>
<td>Compound found in vegetables</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Su-Hyeong &amp; Shivendra (2009)</td>
</tr>
<tr>
<td>Baicalin</td>
<td>Polyphenol (component of PC-SPES)</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Chen et al. (2001)</td>
</tr>
<tr>
<td>Baicalein</td>
<td>Polyphenol (component of PC-SPES)</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Chen et al. (2001)</td>
</tr>
<tr>
<td>Thymoquinone</td>
<td>Component of herbs</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Kaseb et al. (2007)</td>
</tr>
<tr>
<td>Gum mastic</td>
<td>Natural resin</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>He et al. (2006)</td>
</tr>
<tr>
<td>Acetyl-11-keto-b-boswellic acid (AKBA)</td>
<td>Natural resin</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>Inhibition of Sp1</td>
<td>Yuan et al. (2008)</td>
</tr>
<tr>
<td>Selenium</td>
<td>Organic selenium-containing compounds</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Lee et al. (2006)</td>
</tr>
<tr>
<td>Methylseleninic acid (MSA)</td>
<td>Organic selenium-containing compounds</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Chun et al. (2006)</td>
</tr>
<tr>
<td>1,4-Phenylenebis(methylene)selenocyanate</td>
<td>Organic selenium-containing compounds</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Nicole et al. (2010)</td>
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<tr>
<td>Methylseleninic acid (MSeA)</td>
<td>Organic selenium-containing compounds</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>Inhibition of Sp1</td>
<td>Husbeck et al. (2006)</td>
</tr>
<tr>
<td>Selenite</td>
<td>Nonorganic selenium-containing compounds</td>
<td>LNCaP</td>
<td></td>
<td>Transcription</td>
<td>Inhibition of Sp1</td>
<td>Husbeck et al. (2006)</td>
</tr>
</tbody>
</table>

**Table 2: Agents involved in androgen receptor expression**
Table 2 Continued

<table>
<thead>
<tr>
<th>Small molecule</th>
<th>Major function</th>
<th>Cells</th>
<th>Effect</th>
<th>Action level</th>
<th>Supported mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>COX2 inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>Activation of c-Jun</td>
<td>Pan, et al. (2003)</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>COX2 inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>Activation of c-Jun</td>
<td>Pan, et al. (2003)</td>
</tr>
<tr>
<td>Sulindac sulfide</td>
<td>Non-steroidal anti-inflammatory drug</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>Activation of c-Jun, inhibition of Sp1, NF1 and CREB</td>
<td>Lim, et al. (2003)</td>
</tr>
<tr>
<td>CP248, Potent analogs of exisulind</td>
<td></td>
<td>LNCaP</td>
<td>Transcription</td>
<td>Activation of c-Jun, inhibition of Sp1, NF1 and CREB</td>
<td>Lim, et al. (2003)</td>
</tr>
<tr>
<td>CP461, Potent analogs of exisulind</td>
<td></td>
<td>LNCaP</td>
<td>Transcription</td>
<td>Activation of c-Jun, inhibition of Sp1, NF1 and CREB</td>
<td>Lim, et al. (2003)</td>
</tr>
<tr>
<td>Suberohydroxamic acid</td>
<td>HDAC inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>NA</td>
<td>Rokhlin, et al. (2006)</td>
</tr>
<tr>
<td>Depsipeptide</td>
<td>HDAC inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>NA</td>
<td>Rokhlin, et al. (2006)</td>
</tr>
<tr>
<td>Sodium butyrate</td>
<td>HDAC inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>NA</td>
<td>Kim, et al. (2007)</td>
</tr>
<tr>
<td>Suberoylanilide hydroxamic acid (SAHA, vorinostat)</td>
<td>HDAC inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>NA</td>
<td>Marrocco, et al. (2007)</td>
</tr>
<tr>
<td>Parthenolide</td>
<td>NFkB inhibitor</td>
<td>LNCaP, 22Rv1</td>
<td>Transcription</td>
<td>Inhibition of NFkB induced by IL8</td>
<td>Seaton, et al. (2008)</td>
</tr>
<tr>
<td>BAY11-7082a</td>
<td>NFkB inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>Inhibition of NFkB induced by IL8</td>
<td>Seaton, et al. (2008)</td>
</tr>
<tr>
<td>JNK inhibitor I</td>
<td>JNK inhibitor</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>Inhibition of AP-1</td>
<td>Seaton, et al. (2008)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Anticancer drug (anthracyclin)</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>Rokhlin, et al. (2006)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Anticancer drug (topoisomerase II inhibitor)</td>
<td></td>
<td>Transcription</td>
<td>NA</td>
<td>Liu &amp; Yamauchi (2010)</td>
</tr>
<tr>
<td>Anti-b2-microglobulin polyclonal antibody</td>
<td>Antibody</td>
<td>LNCaP, C4-2</td>
<td>Transcription</td>
<td>NA</td>
<td>Huang, et al. (2008)</td>
</tr>
<tr>
<td>Anti-b2-microglobulin monoclonal antibody</td>
<td>Antibody</td>
<td>LNCaP, C4-2</td>
<td>Transcription</td>
<td>Inhibition of SREBP-1</td>
<td>Huang, et al. (2010)</td>
</tr>
<tr>
<td>Dibenzoylmethane</td>
<td>3-Diketone</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>NA</td>
<td>Jackson, et al. (2007)</td>
</tr>
<tr>
<td>Functional domain of saposin C</td>
<td>Neurotrophic peptide</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>NA</td>
<td>Ding, et al. (2007)</td>
</tr>
<tr>
<td>3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole</td>
<td>Triazole derivative</td>
<td>LNCaP</td>
<td>Transcription</td>
<td>NA</td>
<td>Loiarro, et al. (2011)</td>
</tr>
</tbody>
</table>

NA, not available.

aWhen IL8 was added to serum-free media; C/K, up/downregulation of androgen receptor.

AR overexpression in prostate cancer · M Shiota and others
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 (Hawksworth 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 tetradecanoxylation-phorbo1 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)G(A/G)-C(A/T)(T/A)G(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′-TTGGTTAC-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 (Rooste & 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 (PURz) 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). PURz 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 PURz 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 PURz and heterogeneous nuclear ribonucleoprotein-K (hnRNP-K), through binding to a specific sequence (repressor element) in the AR gene 5′-untranslated region. Furthermore, PURz expression was decreased in CRPC cells and tissues, implicating it in the pathogenesis of CRPC (Wang et al. 2008).

PURz expression is attenuated in CRPC cells compared with androgen-dependent PCa cells (Inoue et al. 2008). Recent studies demonstrated that overexpression of PURz in PC-3 and DU145 cells repressed their proliferation *in vitro* (Wang et al. 2008). Intriguingly, PURz 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).

**NFκB**

NFκB (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). NFκB regulates the expression of genes controlling cell proliferation and survival. Aberrant activation of NFκB is frequently seen in many cancers, and induces the expression of genes promoting cell proliferation and protecting against apoptosis. Conversely, defects in NFκB result in suppression of cell growth and increased susceptibility to apoptosis, leading to increased cell death. NFκB inhibition can suppress tumor growth, induce apoptosis, and sensitize cells to anti-cancer agents in various cancers.

NFκB 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 NFκB 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 NFκB (Zhang et al. 2004).

Several studies have examined the expression of NFκB in PCa, and its relationship to clinical features. NFκB was overexpressed in prostatic intraepithelial neoplasia and PCa compared with benign epithelium (Sweeney et al. 2004), and recent studies found that NFκB expression was predictive of biochemical recurrence in patients with positive surgical margins after radical prostatectomy (Ismail et al. 2004). Nuclear localization of NFκB 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 NFκB is frequently activated in PCa, and that its expression may be related to progression. NFκB is constitutively activated in CRPC xenografts where AR expression is also upregulated, suggesting a positive correlation between NFκB 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 knockdown 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 & Wieczorek 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 (Ettenger et al. 2004). Intriguingly, 5α-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 knockdown, 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 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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