

ANDROGENS AND ANDROGEN RECEPTOR IN PROSTATE AND OVARIAN MALIGNANCIES

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1. ABSTRACT

The molecular and biochemical mechanisms contributing to the development and progression of both prostate and ovarian carcinogenesis are currently unknown. A better understanding of the cross-talk between endocrine, signal transduction and regulatory pathways in normal and neoplastic prostatic and ovarian tissues is necessary to elucidate malignant progression in these tissues. This review compares these two malignancies with reference to androgens and the androgen receptor. In particular, the expression and relevance of androgen-regulated genes are discussed. Cytokines, co-activators and co-regulators that interact or effect the androgen receptor are also considered. With increased understanding of the molecular mechanisms of prostate and ovarian carcinogenesis, the identification and development of novel and existing biomarkers may become more achievable.

2. INTRODUCTION

Prostate cancer and ovarian cancer are two examples of gender-specific endocrine malignancies. Prostate cancer is the most common non-cutaneous cancer

diagnosed in men in the United States and is second only to lung cancer with regard to cancer-related deaths (1). The use of prostate-specific antigen (PSA) serum testing in conjunction with a digital rectal examination of the prostate has facilitated the earlier detection of prostate cancer. While there are still controversies related to the reliability of PSA screening, it is generally accepted that serum PSA levels are extremely useful in monitoring the response to treatment and the progression of prostate cancer to an androgen independent stage.

Ovarian cancer is the sixth most common malignancy among women in the United States and is the leading cause of death from gynaecological malignancies (2). The poor survival rate of this malignancy is largely due to the fact that many ovarian carcinomas are detected at an advanced stage and although most respond well initially to chemotherapy, drug-resistant recurrent disease is also apparent (3). Screening tests using cancer antigen 125 (CA125) are available for detection of recurrence of ovarian cancer in some patients and for the detection of most advanced cases (4). Currently there is not a reliable

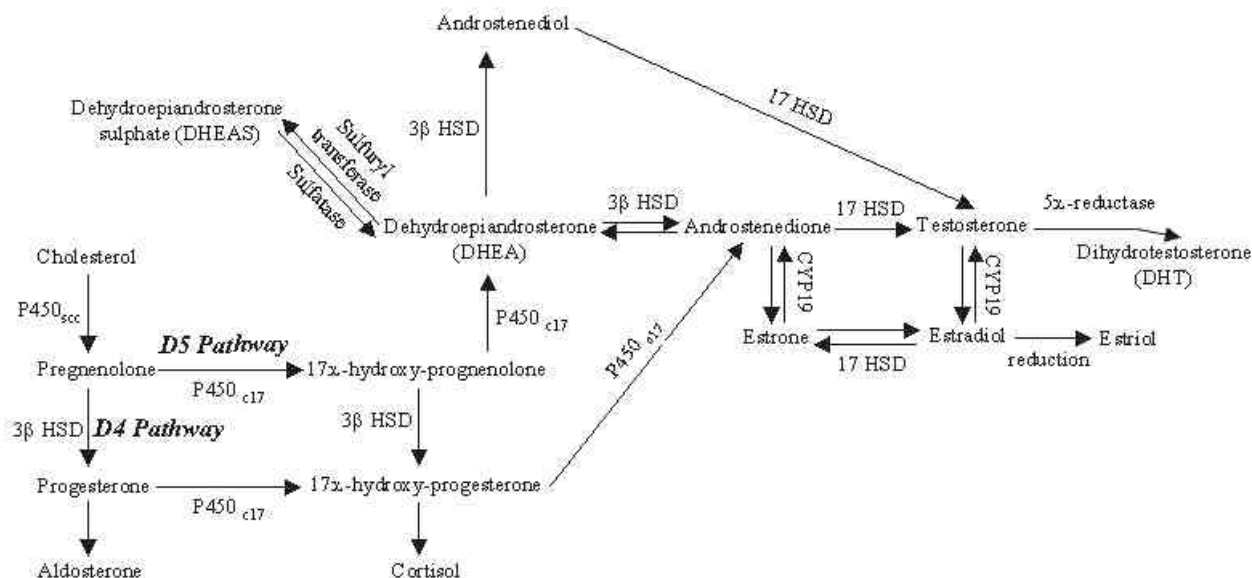


Figure 1. Biosynthesis and metabolism of androgens. Abbreviations: 3βHSD, 3-beta-hydroxysteroid dehydrogenase-Δ5,4-isomerase; 17 HSD, 17-alpha-hydroxysteroid dehydrogenase (7, 19 - 21).

protocol for the detection of early stage disease besides some genetic tests (5).

Despite the high morbidity and mortality from both ovarian and prostate cancers, their etiologies remain obscure (6, 7). The only exception being that hormone levels in the body seem to play a critical role in both malignancies. This review discusses similarities and differences between ovarian and prostate cancer with reference to androgens and the androgen receptor (AR).

3. ANDROGEN BIOSYNTHESIS

3.1. Androgen biosynthesis in men

Androgens, such as testosterone, are steroid hormones which in men are formed primarily in the testes (95%) and the adrenal gland (5%). Formation of androgens in endocrine glands occurs by two biosynthetic pathways (Figure 1) (7). Examples of androgens in adult males are testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone, and androstenediol. In the prostate, DHT is the most potent androgen and is required for growth, development, and secretion (8, 9). The concentration of DHT can be as high as 250 nM in the nuclei of prostatic cells (10). DHT is primarily a peripheral product of metabolism of testosterone that is catalyzed by the enzyme 5α-reductase. Of the two known isoforms of 5α-reductase, type II predominates in the prostate and is coded by SRD5A2 gene on chromosome 2p23 (11, 12). 5α-reductase type I has also been detected in prostatic epithelial cells (13). Finasteride is a type II 5α-reductase inhibitor that has shown efficacy for treatment of benign prostatic hyperplasia (14-17). Finasteride decreases levels of DHT in the serum by 70% and in the prostate by 85-90% (12). Currently, finasteride is being evaluated in a large-scale clinical trial for the prevention of prostate cancer.

In the circulation only approximately 2-3% of testosterone exists in a bioavailable free-form with the majority of this hormone bound to proteins in the serum. These serum proteins are sex hormone-binding globulin (SHBG), albumin and corticosteroid-binding protein (18). SHBG has a high affinity for testosterone and regulates the amount of free testosterone to tissues including the prostate (18).

3.2. Androgen biosynthesis in women

Circulating androgens can be converted to estrogens in peripheral tissues by the enzyme aromatase (CYP19) (Figure 1) (19-21). The major androgens synthesised in women are dehydroepiandrosterone sulphate, dehydroepiandrosterone, and androstenedione (22). Testosterone and DHT are also synthesised but at significantly lower concentrations compared to those produced in men. In women, androgen biosynthesis occurs both in the adrenal and in the ovary glands. Androgens are formed peripherally by two cytochrome P450 enzymes, cholesterol side-chain cleavage enzyme (SCC) and CYP17 (22). Patients with ovarian cancer have serum levels of CA125 that correlate strongly with SHBG and may be related to tumor burden (23).

4. RISK ASSOCIATED WITH INCREASED ANDROGEN LEVELS IN CANCER

4.1. Androgen levels and prostate cancer

Androgens mediate a wide range of developmental and physiological responses and are involved in male sexual differentiation, maintenance of spermatogenesis, and male gonadotropin regulation (24-26). When androgens increase in males during puberty there is an increase in growth of the prostate gland (27).

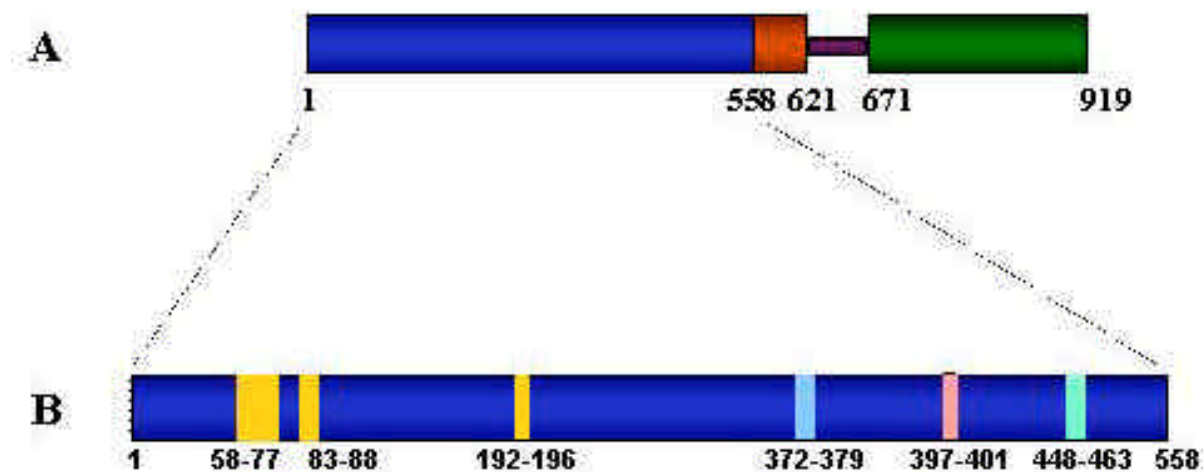


Figure 2. Functional domains of the androgen receptor (66, 67). (A) The AR is comprised of a N-terminal domain (■), a DNA binding domain (■), a ligand binding domain (■), and a hinge region (■). (B) The N-terminal domain contains homopolymeric repeat regions which are thought to influence transactivation of the AR. Examples of these include glutamine repeats (■), proline repeats (■), alanine repeats (■), and glycine repeats (■).

Several lines of evidence indicate that androgens are associated with the development of prostate carcinogenesis. Firstly, androgens induce prostatic carcinogenesis in rodent models (28, 29) and men receiving androgens in the form of anabolic steroids have a higher incidence of prostate cancer (30-32). Secondly, prostate cancer does not develop if humans or dogs are castrated before puberty (33, 34). Castration of adult males causes involution of the prostate and apoptosis of prostatic epithelium while eliciting no effect on other male external genitalia (35, 36). Thus the prostate gland is an androgen-dependent organ where androgens are the predominant mitogenic stimulus (37). This dependency on androgens provides the underlying rationale for treating prostate cancer with chemical or surgical castration (hormone ablation).

Although there is an abundance of biological data that suggests an important role for androgens in the development of prostate cancer (38), recent epidemiologic studies have revealed no clear association (7, 39). Few studies provide convincing data of a positive association between progression of prostate cancer and serum levels of androgen (40). Methodological limitations, together with the uncertainty of whether circulating levels of androgens reflect androgenic action within the prostate gland, are possible explanations for the lack of a positive association between the levels of androgen and prostatic malignancy (7). Epidemiologic studies examining susceptibilities and circulating levels of testosterone in different ethnic groups provide conflicting results. Men at high risk for developing prostate cancer, such as Caucasian Dutch men, have been reported to have increased levels of testosterone compared to low risk Japanese men (41). However, other studies did not confirm these data (42, 43). Ethnic-related risk factors may be associated with foetal or adolescent exposure to these hormones since serum levels of testosterone are 47% higher in black women than in white women during pregnancy (44). This suggests that sex hormones may have imprinting effects on the development of prostate cancer.

4.2. Androgen levels and ovarian cancer

The etiology and early events involved in the progression of ovarian carcinomas are among the least understood of all major human malignancies. However, both epidemiological and experimental observations have implicated sex steroids in the pathogenesis and regulation of growth of carcinomas arising from the ovary (45-48). Patients with ovarian cancer have elevated plasma levels of 17 β -estradiol, estrone, progesterone, 20-hydroxyprogesterone, dehydroepiandrosterone sulfate, androstenedione, and testosterone that correlate with tumor volume (49-52). Elevated levels of androgens are associated with an increased risk of developing ovarian cancer (53, 54).

5. ANDROGEN RECEPTOR

The effects of androgens are mediated through the AR. The AR is a member of the nuclear receptor superfamily (55, 56). The AR was first described in 1969 (57) and then later cloned in 1988 by two independent groups (58, 59). The AR gene is located on the X-chromosome at Xq11-12 and lacks TATA and CAAT sequences in the upstream regulatory region (60). This gene contains 8 coding exons which span a length of approximately 90 kb (59, 61). The AR gene has pur/pyr and GC box SP1 binding sites (62) with two initiation sites for transcription that results in the production of two AR transcripts with differing lengths of 3' untranslated sequence that are 10 kb and 8.5 kb long (60, 63, 64). The AR protein consists of 910-919 amino acids and has a theoretical molecular weight of 98 kDa (65), but runs as a 110-112 doublet in denaturing gel electrophoresis.

The AR protein consists of three functional domains: the amino-terminal domain (NTD), the DNA-binding domain (DBD) and the ligand-binding domain (LBD) (Figure 2) (66). The NTD is coded by exon 1 and comprises almost one-half of the entire AR molecule. The NTD is the most variable between nuclear receptors in

terms of both length and sequence. The AR contains two discrete overlapping regions within the NTD that contribute to transactivation. Ligand-inducible transcriptional activity of the full-length receptor requires activation function 1 (AF-1) that is located between residues 141 and 338 of the NTD (67, 68). A unique feature of the AR is the occurrence of several homopolymeric stretches of amino acids in the NTD. These include a polyglycine tract (24 residues), a polyproline tract (9 residues), and a polyglutamine tract. The length of the polyglutamine tract is polymorphic with the normal variation in repeat length ranging from 11 to 31 trinucleotide units (Figure 2) (69, 70), and a modal length of 20 (71). The length of the glutamine-rich region of the AR affects gene transcription (70, 72). Although a number of studies have demonstrated that men with shorter CAG repeat length are at higher risk of developing prostate cancer, (71, 73-78) others present conflicting data (79-81). In most studies, however, the length of CAG repeats corresponds to racial variation in prostate cancer risk. African Americans, with a high risk for developing prostate cancer, have a shorter CAG repeat length, while Asian men, with a lower risk for developing prostate cancer, have a longer repeat length (69, 82). Consistent with the notion that a shorter repeat length may increase the risk of developing prostatic malignancy, a shorter repeat length is also associated with early onset ovarian cancer (83-85).

The AR DBD is coded by exons 2 and 3 and contains two zinc finger motifs that are essential for binding to sequence specific DNA motifs known as androgen response elements. The hinge region and part of the C-terminal LBD are coded by exon 4. A ligand-dependent bipartite nuclear localization signal is located in the C-terminus of the DBD and the hinge region at residues 617-633. The nuclear localization signal is required for the translocation of the AR to the nucleus (86, 87). The LBD domain is coded by part of exon 4 and all of exons 5-8. The LBD contains a ligand-dependent AF-2 region in helix 12 (88). The AR is unique from other nuclear receptors in the way that AF-1 contributes most, if not all, of the activity to the ligand-bound AR rather than AF-2 (67, 68, 89, 90). The LBD is involved in ligand-binding, dimerization, and interactions with heat-shock proteins and co-regulatory proteins (67, 87, 91). The ligand DHT binds to the wild-type rat AR with highest affinity, with testosterone having 85%, progesterone 24%, 5 α -androstane-3 α and 3 α -androstenediol 17%, 17 β -estradiol 7%, and cortisol 1% relative affinity (92).

Mutations in the LBD can alter the specificity of hormone binding such that transactivation of the AR can take place in the presence of androgens, other steroid hormones, and anti-androgens (93, 94). There is speculation that the use of the anti-androgen, flutamide, may select for cell clones that contain a mutation in codon 877 in the LBD that allows the AR to be activated, rather than inhibited. AR mutations are not a causative factor in tumor initiation due to the low frequency of at which they are detected in localized prostate cancer (95-97). These mutations also do not seem to account for the majority of hormone refractory

prostate cancer. In some cases, castrate levels of androgen may trigger androgenic action in prostate cancer patients receiving androgen ablation treatment which may involve mutated ARs that are hypersensitive to low levels of androgens. For a more complete list of AR mutations see reference (98) and www.mcgill.ca/androgendb. AR mutations have not been extensively examined in ovarian cancer.

5.1. Expression of the AR in prostate and ovarian cancers

The AR is expressed in most histologic types and stages of prostate cancers including primary, metastatic and hormone refractory malignant tissues (99-103). Heterogenous expression of AR, within and among cancer foci, fails to correlate with prognosis (100, 102-105). A common DNA amplification site in recurrent hormone-refractory prostate tumors maps to chromosome Xq11-q13, the site of the AR gene (106). Amplification of the AR gene occurs in 20% to 30% of androgen-independent tumors, but is not typically detected in primary cancers (106-108). Thus, amplification of the AR is associated with relapsing malignancy under conditions of androgen deprivation and thereby suggests that castration is a selection force. Prostate cancer tumors that over-express AR are sensitive to androgens and respond better to second-line maximum androgen blockade therapy than tumors without amplified AR indicating that the overexpressed AR is functional (109, 110). Curiously, the AR has been detected in majority of ovarian cancers (>80%) (84, 111, 112). Estrogen receptor (ER) and the progesterone receptor are detected in less than 50% of ovarian tumors. The expression of AR can be regulated by ERs (113). Specifically, ER α up regulates AR, and ER β down-regulates AR. ER and AR pathways appear to be intertwined and require sequential steps in stimulating the proliferation of luminal epithelial cells of the uterus (113). Expression of AR implies that it has a functional role in ovarian tumors.

5.2. AR signal transduction pathway

The cryptic form of the AR is located in the cytoplasm and nucleus of cells (114-116). After androgen binds to AR, the heat-shock proteins are dissociated from the AR, and the ligand-receptor complex translocates into the nucleus (Figure 3). In the nucleus, the AR binds as a homodimer to the consensus inverted repeat androgen response element, GGTACAnnnTGTTCT, as well as to more complex response elements on the chromosome (117-122). Heterodimers between AR and testicular orphan receptor 4, or ER, have also been reported and in both cases result in a decrease in AR transcriptional activity (123). Transactivation of AR is enhanced by interaction with co-activators on the DNA and modulates the expression of androgen-regulated genes. Although a number of similar co-activators and androgen-regulated genes are also expressed in ovarian cancer, similarities between the mechanisms of action in ovarian cancer cells compared to prostate cancer cells are yet to be elucidated.

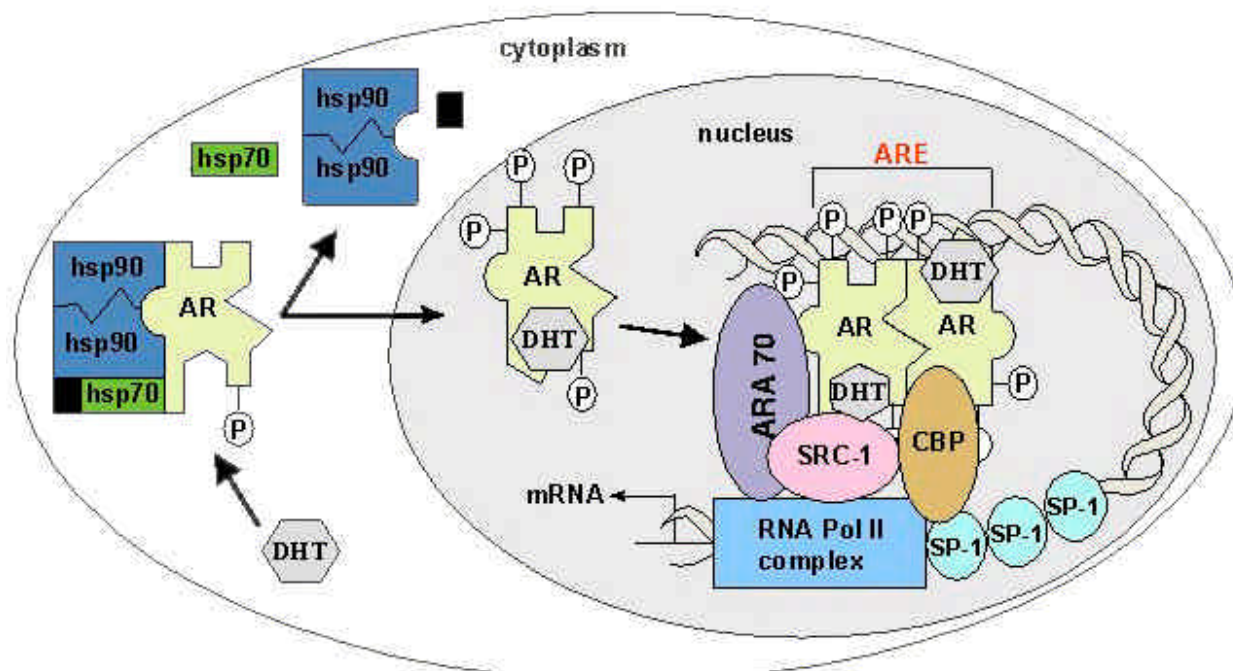


Figure 3. Ligand-dependent activation of the androgen receptor. Androgens such as DHT diffuse through the plasma membrane of the cell and bind to the AR. Upon ligand binding, the AR undergoes conformational changes involving an NH₂-carboxyl-terminal interaction and receptor stabilization. The AR translocates to the nucleus where dimerization and DNA binding to regulatory androgen response elements occurs (114 - 122). AR (androgen receptor); DHT (dihydrotestosterone); CBP (CREB-binding protein); ARE (androgen response element); hsp (heat shock protein); SRC-1 (steroid receptor coactivator 1).

6. ANDROGEN-REGULATED GENES

In the prostate, androgens regulate cell division, differentiation, apoptosis, proliferation, angiogenesis, secretion of proteins and lipid biosynthesis. Using a variety of techniques, differential gene expression in response to androgens has been examined *in vitro* using human prostate cancer cells (124-127). Serial analysis of gene expression (SAGE) detected changes in expression of approximately 136 to 147 genes that were induced and 204 to 215 genes that were repressed in prostate cancer cells in response to androgens (124, 125). cDNA arrays revealed that the expression of 146 to 517 genes were significantly changed by exposing cells to androgens (126, 127). At the protein level, two-dimensional gels measured changes in expression of 44 genes (124). The genes regulated by androgens *in vitro* correspond to the *in vivo* effects of androgens on prostate biology.

One major function of the prostate is to produce seminal fluid. Androgens increase the synthesis and modification of proteins that are secreted by the prostate into seminal plasma such as PSA (124, 126-130), kallikreins 2 and 4 (124, 126, 129, 131, 132), sorbitol dehydrogenase (126, 127), apolipoprotein D (127, 133), and vascular endothelial growth factor (VEGF) (127, 134, 135) as shown in Table 1. Interestingly, expression of some of these genes (such as PSA) has been detected in ovarian cancer (136, 137). A significant correlation between PSA expression and the content of ER in ovarian tumors has

been observed. Despite this, no correlation with histological grading, tumor size or other tumor characteristics in ovarian cancer has been reported (137). Overexpression of KLK4 and apolipoprotein D may be associated with progression of ovarian cancer, particularly late stage serous ovarian cancers (138-140). Elevated expression of vascular endothelial growth factor VEGF has been detected in ovarian cancers and is associated with a poor prognosis (141-144).

Androgens regulate the expression of genes involved in trafficking, vesicular formation, protein folding, glycosylation, polyamine synthesis, and cholesterol and fatty acid metabolism in the prostate. FK506-binding protein is a co-chaperone protein involved in protein folding and trafficking. FK506-binding protein is strongly induced by androgens in the prostate (125-127) and overexpressed in human ovarian cancer (145). Ornithine decarboxylase and downstream enzymes involved in polyamine synthesis are induced by androgens in the prostate (126, 127, 146-149) and elevated levels have been detected in ovarian cancer (150).

Androgens cause changes in the morphology of prostate epithelial cells. As these epithelial cells proliferate they change from a stratified to a cuboidal structure. These changes in morphology require changes in the cytoskeleton and extracellular matrix. In prostate cancer cells, androgens alter the expression of genes involved in these mechanisms such as fibronectin 1 and keratin 8 (124, 126, 127).

Androgen receptor in prostate and ovarian cancer

Table 1. Representative androgen-regulated genes in prostate that are expressed in ovarian malignancies

Gene	Androgen-regulated in prostate	References	Ovarian Cancer	References
Protease/protease inhibitor				
▪ Transmembrane protease serine 2 (TMPRSS2)	+	126, 279,280	-	
▪ kallikrein 2 (KLK2)	+	124, 126, 129, 131	-	
▪ Prostate specific antigen (KLK3)	+	124,126-130	+	136, 137
▪ kallikrein 4 (KLK4)	+	132	+	138
Metabolism				
▪ Sorbitol dehydrogenase (DHSO)	+	126, 127	-	
▪ 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)	+	127, 281	-	
▪ 3-hydroxy-3-methylglutaryl-coenzyme A synthase (HMGCS1)	+	127, 281	-	
▪ Fatty acid synthase (FAS)	+	124, 281	-	
▪ Alpha enolase (ENOA)	+	152	-	
Polyamine Synthesis				
▪ Ornithine decarboxylase (ODC)	+	127, 146-149	+	150
▪ spermine synthase (SMS)	+	126, 127	-	
▪ Spermidine/spermine N1-acetyltransferase (SAT)	+	126, 127	-	
▪ S-adenosylmethionine decarboxylase 1 (AMD1)	+	127	-	
Transport/Trafficking/Ion channels				
▪ FK506-binding protein (FKBP5)	+	125-127	+	145
▪ apolipoprotein D (APOD)	+	127, 133	+	139, 140
Cytoskeleton and Extracellular Matrix				
▪ fibronectin 1 (FN1)	+	126, 127	-	
▪ keratin 8 (KRT8)	+	124, 126, 127	+	151
Proliferation/differentiation/apoptosis				
▪ Inhibitor of differentiation (ID2)	+	126	-	
▪ MAF oncogene (MAF)	+	126, 127	-	
▪ N-Myc downstream regulated (NDRG1)	+	126, 127	+	158
▪ cyclin D1	+	152	+	159, 160
Transcription regulation				
▪ Cyclic AMP-dependent transcription factor (ATF3)	+	126, 127	-	
▪ Homeobox Drosophila family 3 A (NKX3A/NKX3.1)	+	124-127, 152, 155	-	
▪ Prostate epithelium-specific Ets transcription factor (PDEF)	+	125-127	-	
Growth Factors/signal transduction				
▪ Transforming growth factor beta (TGF-β)	+	156	+	161
▪ VEGF	+	127, 134, 135	+	141-144
▪ IGFBP-5	+	152, 153	+	151, 162
▪ Ste-20 related kinase (SPAK)	+	126, 127, 157	-	
▪ Other functions				
▪ transmembrane, prostate androgen-induced RNA (TMEPAI)	+	126, 127, 163	+	168
▪ Adrenomedullin (AM)	+	164	+	162
▪ Clusterin/TRMP2/ApoJ (CLUS)	+	124, 125, 165, 166	+	169
▪ ARA70	+	152	+	170
▪ L-Plastin/lymphocyte cytosolic protein 1 (LCP1)	+	127, 167	+	171

The genes listed in the table are known to be regulated by androgens in prostate tissue and display-altered expression in ovarian cancer cells when compared to non-malignant cells. Positive (+) indicates androgen-regulated expression in prostatic or expression in ovarian tissue and negative (-) indicates that no studies could be located in MEDLINE that determine expression in ovarian tissue.

Expression of keratin 8 is also altered in ovarian cancer (151).

Androgens regulate expression of genes involved in signalling, proliferation, and transcription in prostate cancer cells. These functions involve changes in expression of MAF, N-myc downstream regulated (NDRG1), cyclin D1, ATF3, NK homeobox Drosophila family 3 A (NKX3A), TGF-beta, insulin-growth factor binding protein 5 (IGFBP5), and SPAK (124-127, 152-157). Alternations in NDRG1, cyclin D1, TGF-beta, and IGFBP5 have also been reported in ovarian cancer (151, 158-162). Expression of several other genes that are androgen-regulated in prostate cancer have also been reported to be altered in ovarian cancer. The products of these genes have diverse functions and include: TMEPA1, adrenomedullin, clusterin, L-plastin, and the AR coactivator ARA70 (124-127, 153, 162-171).

Of the genes that have been reported to be androgen-regulated in the prostate, only a handful have been examined for the presence of androgen response elements. For example, PSA (172-175), KLK4 (176), ornithine decarboxylase (147), and L-Plastin (167) have all been reported to contain androgen response elements. This suggests that the AR rather than downstream effects directly regulate these genes. The fact that these genes are also elevated in ovarian cancer may indicate an activated AR in this disease. Unfortunately, specific studies aimed at identifying androgen-regulated genes in the ovary are lacking despite the fact that a high percentage of ovarian malignancies express the AR and androgens appear to be mitogenic (177). In line with the potential of AR underlying proliferation of ovarian cancer, application of anti-androgens inhibit the *in vitro* growth ovarian cancer (178). Blockage of androgen action or synthesis in ovarian cancer cells may have therapeutic value even though the mechanism of action remains unclear. Thus studies examining androgen-regulated genes in the ovary may reveal potential therapeutic targets.

7. CO-ACTIVATORS, CO-REPRESSORS AND OTHER PROTEINS INTERACTING WITH THE AR

7.1. Co-activators

Expression of androgen-regulated genes is affected by co-regulators that influence a number of functional properties of AR, including ligand specificity and DNA-binding capacity (179). Thus co-regulators modify the transcriptional activity of the AR which could theoretically play a role in the aetiology and progression of cancer. At the promoter of target genes, co-regulators participate in DNA modification, either directly through modification of histones or indirectly by the recruitment of chromatin-modifying complexes. Co-regulators also aid in recruitment of the basal transcriptional machinery. Aberrant co-regulator activity due to mutation or altered expression levels may be a contributing factor in the progression of diseases related to AR activity, such as prostate cancer and possibly ovarian cancer. AR demonstrates distinct differences in its interaction with co-

regulators from other steroid receptors due to differences in the functional interaction between AR domains. To date more than 30 proteins have been identified as being a co-activator of the AR and these are described in more detail elsewhere (for a recent review see reference 179).

7.1.1. SRC-1 (NCoA-1)

The first identified member of co-activators that regulate steroid receptor action was steroid receptor co-activator 1 (SRC-1) (180). Phosphorylation of SRC-1 by MAPK is required for optimal progesterone receptor-dependent transcription and for functional cooperation with CREB-binding protein (CBP) (181). SRC-1 interacts with both AF-1 and AF-2 of the AR and enhances ligand-dependent and ligand-independent transactivation to increase transcription of androgen-regulated genes (182-184). Patients with androgen-independent prostate cancer have elevated levels of SRC-1 (185, 186) and MAPK activity (187) in tumor cells. Phosphorylation of SRC-1 by MAPK is required for optimal ligand-independent activation of the AR by interleukin-6 (IL-6). Protein-protein interaction between endogenous AR and SRC-1 is dependent upon exposure of prostate cancer cells to IL-6 or androgen and independent of MAPK (182). Ligand-independent activation of the AR does not occur by a mechanism of solely overexpression of either wild-type SRC-1 or a mutant SRC-1 that mimics its phosphorylated form (182).

7.1.2. ARA54, ARA55, and ARA160

The ligand-bound AR regulates target genes via a mechanism that may involve co-regulators such as ARA54, 55 and 160. Dominant-negative co-regulators of the AR are capable of suppressing AR transactivation and cell proliferation in prostate cancer cells which may provide new therapeutic approaches for blocking AR-mediated proliferation of prostate cancer (188). ARA54 and ARA55 enhance the androgenic effects of 17 β -estradiol and the anti-androgen hydroxyflutamide, which is commonly used in the treatment of prostate cancer (189-192). ARA160, an AR N-terminal interacting protein also known as TATA element modulatory factor (TMF), co-operates with ARA70 to enhance androgen-induced AR activity (190, 191). ARA54, ARA55, and ARA160 have not been described in ovarian cells.

7.1.3. ARA70

ARA70 is a reported co-activator that enhances transactivation of the AR at least 10-fold in both ovarian and prostate cancer cells (189, 193-198). In a study using LNCaP prostate cancer cells, ARA70 enhanced transactivation of the AR in response to androgen and estradiol (191). Altered ARA70 expression may also lead to antiandrogens mediating paradoxical agonist effects on the AR (199). Increased expression of ARA70 has been reported in ovarian cancer cells (200). Together, this suggests that amplification of transactivation of the AR by increased expression of ARA70 may be involved in the etiology/progression of ovarian and prostate cancers as well as underlying antiandrogen withdrawal syndrome.

7.1.4. BRCA1

The breast cancer susceptibility gene, BRCA1, is located at chromosome 17q21 and codes for a protein comprised of 1,863 amino acids (201). The gene product of BRCA1 is a nuclear phosphoprotein that plays a role in the (i) regulation of cell proliferation; (ii) DNA repair; and (iii) regulation of transcription (202-204). BRCA1 enhances transactivation of the AR by a mechanism involving physical interaction and the NTD of the receptor (205). This results in the increased transcription of androgen-regulated genes (205, 206). Overexpression of p160 coactivators, such as SRC-1, potentiate the effects of BRCA1 upon transactivation of the AR (205). Loss-of-function, germline mutations of BRCA1 predispose to hereditary ovarian cancer (207-213) and possibly prostate cancer (214-220). Patients with ovarian cancer that have mutated BRCA1 tend to experience better survival over those who do not have mutated BRCA1 (221). Whether such advantages of a mutated BRCA1 gene in regard to survival is due to effects upon transactivation of the AR are currently unknown. Disease-associated mutations do however reduce the ability of BRCA1 to enhance transactivation of the AR.

7.1.5. SRC-3 (Rac-3, ACTR, AIB1, p/CIP, TRAM)

SRC-3 is a nuclear receptor coactivator that interacts with the AR to enhance transactivation (222, 223). Like other members of the SRC family, SRC-3 possesses acetyltransferase activity which may aid in establishing or maintaining an open chromatin structure at the promoter of nuclear receptor target genes (224). Epidemiologic studies investigating the role of SRC-3 in prostate cancer have yielded conflicting results. Some studies show a positive association between SRC-3 and its CAG repeat length and prostate cancer (225, 226), while others report no association (227). Further research is required to elucidate the role of this co-activator in relation to carcinogenesis of the prostate. In ovarian cancer, DNA amplification at the chromosomal region where SRC-3 is located (20q12-q13) has recently been described (228-230). Amplification of SRC-3 is associated with expression of ER in sporadic ovarian carcinomas (230). A high frequency of gene amplification at 20q12-q13.2 suggests that the genes amplified therein may play a central role in the pathogenesis of sporadic and hereditary ovarian carcinoma (229).

7.2. Co-repressors

In comparison to co-activators, few co-repressors of the AR have been identified. Two examples are calreticulin and cyclin D1. These molecules interact with the AR DBD to inhibit binding of the AR to androgen response elements and thereby block transcription (231-233). Interestingly both calreticulin and cyclin D1 have been reported to be androgen-regulated (152, 234) and cyclin D1 is overexpressed in ovarian cancer (159, 160). The role of co-repressors of the AR in cancer is currently unknown.

7.3. Other proteins interacting with the AR

In addition to co-activators and co-repressors, the AR has been shown to interact with transcription factors

such as members of the activation protein-1 (AP-1) family (235-237), nuclear factor kappa B subunit (NFkB) (238, 239), SMAD3 (240), sex-determining region Y (241), Ets family member proteins (ERM) (242) and signal transducer and activator of transcription 3 (STAT3) (182, 243, 244). Interaction between the AR and these transcription factors either enhances or inhibits transactivation. Of particular interest is the interaction of the AR with STAT-3 due to the increasing clinical implications of elevated levels of IL-6 in the serum of patients with both prostate and ovarian cancers. STAT3 is a transcription factor involved in IL-6 signal transduction and has been shown to be important for the progression of prostate cancer cells (245), induce transformation of cells (246), and interact with the AR NTD to increase transactivation of the AR in the absence of androgens (243). STAT-3 is constitutively activated in ovarian cancer (247). For a more complete list of proteins that interact with the AR, see ww2.mcgill.ca/androgendb/Arinteract.pdf.

8. INTERLEUKIN-6

IL-6 has gained considerable clinical interest in both prostate and ovarian cancers. This cytokine is multi-functional and plays an important role in the regulation of hematopoiesis, immune response, inflammation, bone metabolism, and neural development (248). IL-6 is produced by lymphoid, non-lymphoid cells and cancer cells (249). IL-6 appears to play a potential role in prostate and ovarian cancers by a mechanism that may involve STAT3 and/or ligand-independent activation of the AR. Whether the AR mediates the effects of a dysregulated IL-6 pathway in prostate and ovarian cancer is currently unknown but warrants further investigation.

8.1. IL-6 and prostate cancer

Prostate cancer predominately metastasizes to bone that expresses IL-6 (250, 251). Prostate epithelial cells from normal, hyperplasia and carcinoma tissue also express IL-6 (252). IL-6 mediates its effect by binding to the IL-6 receptor. The IL-6 receptor has been detected in normal prostate, high-grade prostatic intraepithelial neoplasia and cancer (253, 254). Circulating levels of IL-6 are elevated in patients with metastatic prostate cancer (252, 255) and hormone refractory disease (256). Prostate cancer cells proliferate more rapidly in response to IL-6 (243, 257-259) with neutralizing antibody inhibiting the proliferation of PC-3 and DU 145 prostate cancer cells (260-262). In prostate cancer cells, IL-6 has been shown to cause ligand-independent activation of the AR by a mechanism involving protein-protein interactions between the AR NTD and STAT-3 (243).

8.2. IL-6 and ovarian cancer

IL-6 is found in the normal ovary, where it may participate in follicle development by reducing the follicle-stimulating hormone binding capacity of granulosa cells (263, 264). IL-6 stimulates the growth of ovarian carcinomas and is produced by these cells (265, 266). Although little is known about the regulation of cytokine expression in ovarian surface epithelium, it is known that these agents have regulatory effects on follicular growth,

differentiation, and ovulation (267, 268). Increased expression of cytokines such as IL-6 occurs in ovarian cancer (269). Two major sources of IL-6 production at ovarian tumor sites are peritoneal mesothelial cells and cancer cells (270). A high percentage of ovarian cancers overexpress the p53 protein, which has been shown to regulate expression of IL-6 *in vitro* (271). A recent *in vitro* study using ovarian surface epithelial cells and ovarian cancer cells demonstrated that IL-6 enhanced proliferation, while antibodies to IL-6 partially inhibited proliferation of ovarian cells (272). Serum levels of IL-6 are elevated in patients with ovarian cancer (265, 273-277), but CA125 is still considered to be a more sensitive biomarker (265, 277). However, serum IL-6 levels may be associated with the extent of residual disease and clinical outcome (274, 277, 278). A high level of IL-6 appears to result in prolonging survival of tumor cells and promoting resistance to chemotherapy by blocking apoptosis. One possible underlying mechanism may involve transactivation of the AR by IL-6 as seen in prostate cancer, but to date this has not been explored.

9. PERSPECTIVE

Both ovarian and prostate malignancies are multifactorial diseases, contributing to the difficulties associated with determining underlying mechanisms. Elevated levels of androgens may play a significant role in the development of prostatic and ovarian carcinogenesis. Altered expression, polymorphisms in the length of the CAG repeat, and mutations of the AR may also be involved in the development and progression of these malignancies. Androgens are capable of regulating genes that display altered expression in prostate and ovarian cancers and function to promote the growth of the tumor. Androgen-regulated genes that may be involved in cell proliferation may act both directly and indirectly and in combination with an array of other molecules including co-activators, co-repressors, cytokines and growth factors. There is a great need for enhanced understanding of the molecular mechanisms that control growth and differentiation of prostatic and ovarian epithelium. Improved understanding of biological processes will lead to development of novel therapeutic techniques and identification of superior, clinically useful biomarkers markers.

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