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Local Endocrine, Paracrine and Redox Signaling Networks Impact Estrogen and Androgen Crosstalk in the Prostate Cancer Microenvironment

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Abstract

Androgen receptor (AR) signaling is essential for the initial development and progression of prostate cancer (PCa) as well as the growth and survival of castration-resistant tumors. However, AR action may be opposed by estrogen receptor beta (ERβ) that responds to androgen metabolites produced in the prostate. The balance between the activity of these two receptors is not only influenced by the steroidogenic capacity of the prostatic microenvironment but also by its redox status and local paracrine signals such as transforming growth factor- beta (TGF-β). In this review, we highlight the studies that revealed select roles for AR and ERβ in distinct compartments of the prostate cancer microenvironment. We also discuss new work that identified stromal-epithelial crosstalk through TGF-β1 signaling that drives the production of reactive oxygen species in stromal cells thereby selectively limiting the antitumor activity of ERβ in cancer cells. Therefore, any new therapeutic approaches that seek to limit AR but enhance ERβ activity in PCa, must take into account potential adaptive changes in the tumor microenvironment that utilize paracrine signals and altered redox balance to divert local androgen metabolites towards AR at the expense of ERβ.

Keywords

androgen receptor; estrogen receptor-beta; prostate cancer; reactive oxygen species; transforming growth factor-beta; tumor microenvironment

Androgen signaling is crucial for the stimulation of new cell growth and development in prostate epithelial cells, which undergo a constant low level of turnover. Due to this growth and developmental function of androgen receptor (AR), it is to be expected that in prostate cancer (PCa) an abundance of AR signaling underlies the overgrowth of epithelial cells seen in carcinogenesis. During early stages of the disease, multiple factors can contribute to the hyperactivity of AR. Mutations within the AR gene can lead to a more promiscuous receptor that can be activated in the absence of ligand, or by additional growth factors such as epidermal growth factor and insulin-like growth factor-1 [1–5]. Increased expression of AR-

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specific co-activators and/or alterations in post-translational modifications can also be the source of aberrant AR signaling in early PCa [6].

While initial therapy for PCa is removal of the organ, recurrent disease is a common problem. Without a localized target tissue, the recurrent cancer cells, which are still dependent upon androgen signaling for continued growth, are typically targeted through systemic androgen deprivation [7]. This chemical castration is achieved by administration of a gonadotropin releasing hormone agonist or a specific AR-antagonist [8,9]. The former two lead to an overall decrease in endogenous production of androgens, whereas the latter targets the ability of circulating androgens to effectively activate the AR. This chemical castration is initially effective, but after prolonged androgen deprivation eventually the metastatic disease becomes castration resistant and unresponsive to this therapeutic approach [10]. Castration-resistant PCa (CRPC), however, is still dependent upon AR signaling; it is the therapeutic approach to ablating androgen activation that loses efficacy, as aberrant AR activation resumes despite the modalities employed for chemical castration [11]. Patients with CRPC still exhibit activation of AR target genes (e.g. prostate specific antigen or PSA), thus demonstrating that AR is still active in the course of the disease despite a therapeutic attempt to remove potent circulating androgens.

Recent studies using an intricate series of highly specific AR-knockouts in mice reveal the complicated the role of AR in PCa and generated some unresolved controversy. Specifically, Niu et al. have suggested that AR in the prostatic epithelium is tumor suppressive, whereas AR in prostatic stromal cells promotes invasion by a cancerous epithelium [12]. Additional follow-up of these results led to the hypothesis that one of the mechanisms through which AR alters epithelial invasive characteristics is through modulation of transforming growth factor-beta (TGF-β) signaling. A subset of TGF-β responsive genes, including the inducible pro-inflammatory enzyme cyclooxygenase-2 (COX-2), is not upregulated following TGF-β treatment when AR is stably re-expressed in PC3 PCa cells [12]. These TGF-β responsive genes act to promote tumor aggressiveness, thus inhibiting their induction via reexpression of AR provides tumor-suppressive activity. Androgen signaling, even in castration-resistant disease, appears to be a double-edged sword. Clearly, studies such as these would argue against global androgen deprivation therapy, again underscoring the need for a more thorough understanding of PCa growth and progression to develop more targeted and efficacious therapies.

As men age, serum testosterone levels naturally decline and the main source of androgens shifts to the adrenal gland, whose major androgen product is dehydroepiandrosterone (DHEA) [13]. However, a concomitant equilibrium of estrogen levels leads to decrease in the testosterone to estrogen ratio [14]. Thus, recent attention has been paid to understanding the balance between androgenic and estrogenic signaling in prostate biology (Figure 1). There are type distinct estrogen receptors (ERs), designated as ERα and ERβ. Unlike AR, whose activation is associated with prostate growth, signaling through ER appears to be more complex, due in large part to differential activities of the ER subtypes. ERα activation in the prostate is associated with three distinct responses: aberrant proliferation, inflammation, and cancer [15]. Aromatase knockout mice have lifelong elevated levels of androgens, yet the mice fail to develop PCa [16]. However, administration of synthetic estrogens early in development triggers abnormal prostate biology later in life in these knockout mice [17].

While these studies suggest that ERα signaling may be associated with the development of PCa, the prevailing ER subtype in the prostate is ERβ [18,19]. Knockout mice have been generated that are deficient only in the ERβ subtype, and extensive studies performed with these mice have shown that while ERα mediates estrogen-induced prostatic inflammation

and pathologies, ERβ may confer a beneficial effect in maintenance of normal homeostasis [15]. Supporting epidemiological evidence also exists, as men who consume higher dietary intakes of phytoestrogens (weakly estrogenic compounds that exhibit a significantly higher affinity for ERβ over ERα) exhibit a lower incidence of PCa [20,21].

A unique feature of ERβ is its sensitivity to oxidation. This reportedly high redox sensitivity of ERβ may be important in tumors or tissues exposed to chronic inflammation. In particular, chronic inflammation leads to increased levels of reactive oxygen species (ROS) and subsequent development of an oxidizing milieu. Keeping this in mind, the oxidation-sensitive motifs in ERβ may be of particular relevance in PCa. Kumar et al. showed that oxidative stress in PCa cells is required for an aggressive phenotype, and that PCa cells are capable of generating high levels of ROS [22]. Recent work from our laboratory showed that prostate stromal cells are also capable of generating ROS in response to locally produced TGF-β1 [23].

Zinc-finger motifs containing 4 cysteine residues are an essential feature of the DNA-binding domain of members of the nuclear receptor superfamily of transcription factors [24]. In ERβ, as in other nuclear receptors, the first zinc-finger is necessary for DNA binding and the second zinc-finger contributes to receptor dimerization, an essential step for stabilization of DNA binding at the promoter [24,25]. ERβ oxidation can occur within the 2nd zinc finger motif, leading to a conformational change that destabilizes the receptor and ultimately prevents DNA binding [25,26]. Electrophoretic mobility shift assays have demonstrated a loss of DNA-binding when ERβ is subjected to oxidation by H_2O_2 [25]. As Figure 2 illustrates, more recent work from our laboratory using chromatin immunoprecipitation assays demonstrated a direct decrease in ERβ occupancy at the E-cadherin promoter in PCa cells exposed to H_2O_2 [23]. This is in accordance with ERβ work done in breast cancer that demonstrated a restoration of ERβ DNA-binding capacity following treatment with the thiol reducing agent dithiothreitol [27].

Local steroidogenesis is an intricate and tightly controlled process that provides another level of regulation to steroid hormone action beyond that occurring following the binding of ligand to steroid hormone receptors. Differential enzyme expression in various tissues allows metabolism that either activates or inactivates various steroid hormone precursors into ligands that will preferentially bind the steroid hormone receptor of importance in that tissue. In the prostate, for example, the enzyme 5α-reductase is highly expressed. 5α-reductase converts testosterone into dihydrotestosterone (DHT), a ligand much more potent for the AR than testosterone [28,29]. Unlike testosterone, DHT is unable to be converted to estradiol by the enzyme aromatase [30]. Thus, expression of 5α-reductase ensures adequate activation of AR in the prostate while limiting the production of the highest affinity ligand for ER.

Nonetheless, strong evidence exists for both the peripheral and intraprostatic production of estrogens in ageing males [14,15]. However, there is an increasing body of evidence supporting the role of androgen metabolites as the main ligand source for ER-dependent signaling in the prostate [18,31]. Specifically, 2 DHT metabolites, 5α-androstane-3α,17β-adiol (3α-Adiol) and 5α-androstane-3β,17β-adiol (3β-Adiol), have been shown to be potent ERβ ligands [31,32]. The importance of these metabolites as ERβ ligands is underscored by the fact that the local concentration of 3β-Adiol in the prostate is one hundred fold higher than that of estradiol [33].

Activation of ERβ in the prostate is ensured by local tissue expression of the enzymes AKR1C2 and AKR1C3, which are responsible for the metabolism of DHT into 3α-Adiol and 3β-Adiol, respectively [34,35]. Analysis of PCa specimens revealed limited expression

of enzymes responsible for *de novo* steroidogenesis, indicating that the conversion of androgenic precursors is the predominant method of controlling the balance in androgenic and estrogenic signaling pathways [35]. These steroid-converting enzymes are of growing interest in PCa. Polymorphisms in the AKR1C enzymes have been correlated with PCa risk [36], and recent endeavors to identify small molecule modulators of these enzymes have been undertaken using modern high-throughput screening techniques [37].

Epithelial-to-mesenchymal transition (EMT) is a crucial early step in the acquisition of a more motile and invasive phenotype, hence permitting cancer cells to migrate and invade surrounding tissues. Loss of the epithelial marker E-cadherin is a known indicator of EMT, which is associated with loss of cell adhesion and a subsequent increase in cell motility [38]. As ERβ ligands, Adiols initiate a signaling pathway that inhibits cell motility by increasing cell adhesion through induction of E-cadherin expression [32,33,39]. An inverse relationship exists between ERβ expression and the progression of PCa to a high Gleason grade [33]. Tissue staining done by Mak et al. demonstrates that E-cadherin expression is directly correlated with ERβ expression in PCa [33]; thus, loss of ERβ expression is directly associated with increased motility and aggressiveness. Recently published work from our laboratory further supports the role of an Adiol-ERβ pathway in inducing expression of E-cadherin in PCa cells, but with the novel indication that this pathway is sensitive to inactivation via oxidation of ERβ by locally produced ROS [23]. Signaling through Adiol-ERβ appears to be one mechanism through which prostate growth is tightly regulated; hence, this pathway presents a putative target for therapeutic intervention.

One of the overarching themes reviewed herein is the crucial role of oxidative stress in altering steroid receptor signaling within the cancerous prostate. We propose that controlling the redox status of the local milieu may serve to limit the aggressiveness of PCa by influencing steroid receptor signaling. The role of the tumor microenvironment can change from inhibitive to permissive simply by paracrine signals generated by the cancer cells in an effort to escape intrinsic control [23]. Cancer cells themselves are capable of generating significant amounts of ROS that further alter the redox status of their microenvironment [50]. While multiple sources of ROS exist within the prostate, COX-2, a pro-inflammatory enzyme whose expression is generally labile and transient, has been shown to be capable of producing ROS as a byproduct of the 2-step oxidation process of arachidonic acid [40]. PCa cells overexpress COX-2, and consistently high levels of COX-2 are associated with worse prognosis [40,41]. Addition of selective pharmacologic inhibitors of COX-2 has been shown to decrease cancer cell growth, induce apoptosis, and decrease tumor size in animal models [40].

Interestingly, it is not simply COX-2 expression by the cancer cells that is responsible for increased aggressiveness. A xenograft of Lewis lung carcinoma cells (positively expressing COX-2) was unable to form a tumor in a COX-2 −/− host, suggesting that stromal COX-2 is necessary for tumor development in this model. Upon further investigation, it was found that the COX-2 −/− fibroblasts were unable to secrete VEGF, an obligatory requirement for tumor formation [42]. Newer studies in PCa from our laboratory suggest that stromal COX-2 is capable of generating sufficient H_2O_2 to oxidize and inactivate ERβ in nearby cancer cells, ultimately leading to a disinhibition of the inherent motility-suppressing capacity of the prostate stroma on ERβ-expressing PCa cells [23]. In accordance with this molecular basis for stromal COX-2 in PCa, a study by Richardsen et al. showed that high expression of COX-2 in the prostate stroma correlates with decreased disease-specific survival [41]. Not surprisingly, these data have led to clinical trials of Cox-2 inhibitors (i.e. nonsteroidal anti-inflammatory drugs) in PCa, but the results of the trials remain inconclusive and further studies are needed [43,44].

Presumably, another target for therapeutic intervention is to directly target an endogenous regulatory mechanism capable of limiting cancer cell motility. As previously discussed, intraprostatic synthesis of Adiols serves to limit cancer cell motility through ERβ activation. Recent studies have demonstrated that synthetic ERβ ligands can act in a manner similar to endogenously produced Adiol in repressing a gene transcription pathway responsible for inducing an inflammatory response in the microglia [45]. However, while this suggests that synthetic Adiols may represent a potential therapy in the future, additional research is needed to ensure that ERβ is the target receptor.

Future therapies must also be mindful of potential crosstalk between tumor suppressive ERβ and tumor promoting AR. For example, mutated AR such as is often seen in CRPC, is capable of binding 3β-Adiol with a subsequent activation of AR target genes responsible for cancer cell proliferation [46]. Therefore, inactivation of ERβ via oxidation, as our work suggests, could disrupt its crosstalk with AR and tip the balance in favor of AR activation by weak ligands (i.e. Adiols) in vulnerable PCa cells. In this case, a unique cancer-promoting AR gene signature may be influenced by a combination of the steroidogenic capacity and redox status of various components of the tumor microenvironment. Therefore, future therapeutic interventions should seek to maintain ERβ activity in a hostile tumor microenvironment and limit the contributions of AR to PCa progression.

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Abbreviations

3α-Adiol	5α-androstane-3α,17β-adiol,
3β-Adiol	5α-androstane-3β,17β-adiol
AR	androgen receptor
CRPC	castrate-resistant prostate cancer
COX-2	cyclooxygenase-2
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
EMT	epithelial-to-mesenchymal transition
ER	estrogen receptor
PCa	prostate cancer
ROS	reactive oxygen species
(TGF-β	transforming growth factor beta

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Highlights

- Estrogen receptor beta action limits the growth and migration of prostate cancer cells
- Steroid ligands produced in prostatic tissue can activate estrogen receptor beta
- TGF-β generates reactive oxygen species that inhibits estrogen receptor beta

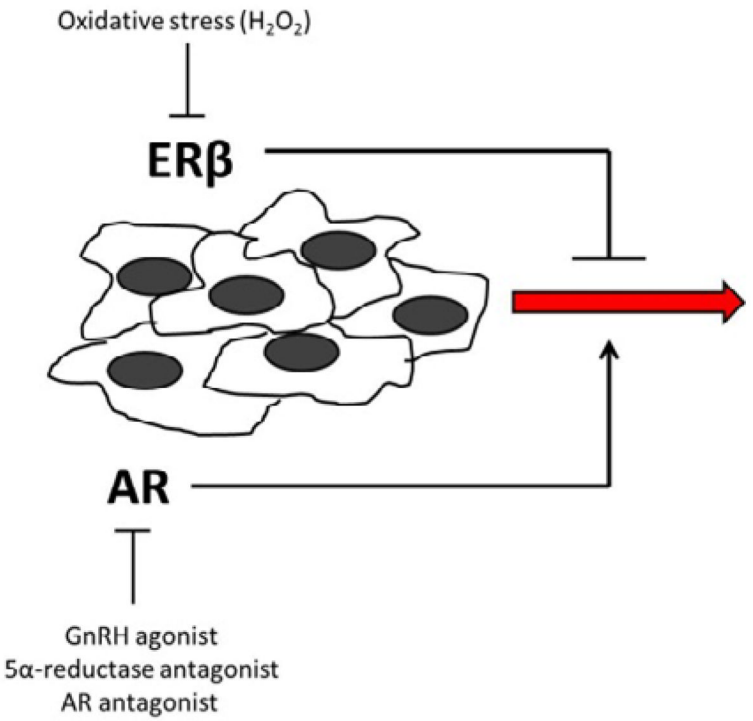

Figure 1. The predominant steroid receptors in the prostate are AR and ERβ

AR acts to enhance cancer cell motility, while ERβ is inherently anti-motility. Systemic therapy targeting AR is used to slow down the progression of cancer, perhaps by tipping the balance towards ERβ signaling. However, local ROS production serves to inactivate ERβ, and thus allows unopposed AR activity. It is the balance in action of these 2 receptors that ultimately can determine the motility of the cancer cells. Thus, therapies targeted at swaying the balance towards ERβ activity may serve to limit cancer cell motility by utilizing an inherent regulatory pathway.

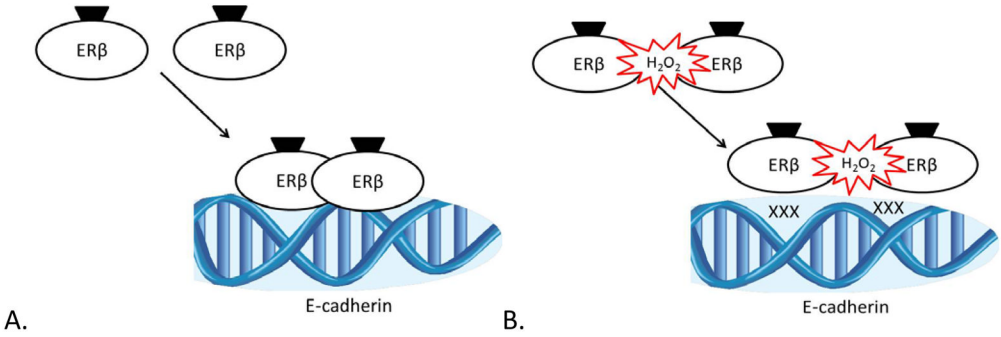

Figure 2. ERβ activity at the E-cadherin promoter in PCa cells

(A) In a redox neutral milieu, ligand binds ERβ and initiates receptor dimerization, occupancy of its cognate DNA-binding element in the E-cadherin promoter, and activation of transcription. (B) In the presence of H_2O_2, ERβ is oxidized at the 2nd zinc-finger motif and is unable to dimerize, thus destabilizing its DNA-binding capacity and leading to a loss of E-cadherin transcriptional activation.