Pro-survival and anti-apoptotic properties of androgen receptor signaling by oxidative stress promote treatment resistance in prostate cancer

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Abstract

Oxidative stress caused by an increase in reactive oxygen species levels or a decrease in cellular antioxidant capacity can evoke the modulation of various cellular events including androgen receptor (AR) signaling via direct or indirect interactions. In this review, we summarize the mechanisms of AR activation by oxidative stress including: i) AR overexpression; ii) AR activation by AR co-regulators or intracellular signal transduction pathways; iii) generation of AR mutations or splice variants; and iv) *de novo* androgen synthesis. AR signaling augmented by oxidative stress appears to contribute to pro-survival and anti-apoptotic effects in prostate cancer cells in response to androgen deprivation therapy. In addition, AR signaling suppresses anti-survival and pro-apoptotic effects in prostate cancer cells in response to various cytotoxic and tumor-suppressive interventions including taxanes and radiation through the modulation of β III-tubulin and ataxia telangiectasia-mutated kinase expression respectively. Taken together, AR signaling appears to render prostate cancer cells refractory to various therapeutic interventions including castration, taxanes, and radiation, indicating that AR signaling is a comprehensive resistant factor and crucial target for prostate cancer treatment.

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Introduction

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of male cancer-related mortality in western countries. A special characteristic of prostate tumors is their dependence on androgen receptor (AR) signaling for their carcinogenesis, development, and progression (Basu & Tindall 2010). Inversely, androgen deprivation therapy, which reduces androgen production, or anti-androgen agents, which interfere with AR function, are gold-standard treatments for recurrent or advanced prostate cancer (Miyamoto *et al.* 2004). However, androgen-dependent prostate cancer eventually develops into castration-resistant prostate cancer (CRPC), which can be attributable to augmented pro-survival and anti-apoptotic properties by AR signaling and others (Niraula *et al.* 2012). Against CRPC, few therapeutics including taxane chemotherapy are not

curative, only ameliorating cancer-caused symptoms and prolonging survival for a few months. Recently, novel AR-targeting agents such as the cytochrome P17 inhibitor abiraterone acetate and the second-generation anti-androgen MDV3100 have been proved to reduce tumor burden and improve overall survival in CRPC patients, although their efficiencies are also limited, prolonging survival for only 3–5 months (de Bono *et al.* 2011, Scher *et al.* 2012).

Reactive oxygen species (ROS) include superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($HO\cdot$), and are produced by the partial reduction of oxygen. Cellular ROS are generated endogenously, mainly during the process of mitochondrial oxidative phosphorylation, or can arise exogenously from xenobiotic compounds. Oxidative stress is caused when the cellular antioxidant defense system is overwhelmed by an increase in ROS levels or

a decrease in cellular antioxidant capacity. This stress leads to the damage of nucleic acids, proteins, and lipids, and has been implicated in various disorders including carcinogenesis (Trachootham *et al.* 2009), neurodegenerative diseases (Andersen 2004), atherosclerosis, diabetes (Paravicini & Touyz 2006), and aging (Haigis & Yankner 2010). Oxidative stress also has effects on the redox regulation of redox-reactive cysteine (Cys) residues in redox-sensitive proteins. Oxidation of these residues forms reactive sulfenic acid (–SOH) that can form disulfide bonds with nearby cysteine residues (–S–S–) or undergo further oxidation to sulfinic (–SO₂H) or sulfonic (–SO₃H) acid. These oxidative modifications change protein structure and thus affect their function. Except where –SO₃H is involved, these redox modifications can be reversed by reducing systems such as thioredoxin and peroxiredoxin (Roos & Messens 2011). Thus, oxidative stress can modulate various cellular actions, including AR signaling, via direct or indirect interactions (Ray *et al.* 2012).

Oxidative stress has been shown to play an important role in the tumorigenesis and progression of prostate cancer (Bostwick *et al.* 2000, Sharifi *et al.* 2008, Khandrika *et al.* 2009), as well as in the conversion of androgen-dependent prostate cancer into CRPC (Sharifi *et al.* 2008, Shiota *et al.* 2010, 2011a). Together, these results suggest an intimate cross-talk between oxidative stress and AR signaling. In this review, we summarize the effects of oxidative stress, which plays pro-survival and anti-apoptotic roles against various prostate cancer treatments, on AR signaling.

Oxidative stress by treatment in prostate cancer

Several experiments in both *in vitro* and *in vivo* have indicated that castration induced oxidative stress through redox imbalance by up-regulating ROS production via NADPH oxidases and down-regulating ROS-detoxifying enzymes such as manganese superoxide dismutase (SOD2; Pang *et al.* 2002, Tam *et al.* 2003, Best *et al.* 2005, Shan *et al.* 2010). Although there are several conflicting studies showing that androgens induce oxidative stress (Pinthus *et al.* 2007, Pathak *et al.* 2008), they may reflect a physiological or non-physiological condition. Ripple *et al.* (1997) reported that the physiological level of androgens decreased oxidative stress while the overloading of androgens induced oxidative stress, suggesting non-specific stress under non-physiological condition. In humans, it was found that androgen

deprivation therapy decreases SOD2 expression in biopsy tissues of prostate cancer (Best *et al.* 2005), and increases oxidative stress in prostate cancer cells as well as in surgically resected tissue of prostate cancer tissues (Shiota *et al.* 2010, 2012). In addition to androgen deprivation, several treatments against prostate cancer including taxane chemotherapy and radiotherapy are known to induce oxidative stress (Acharya *et al.* 2010). Thus, various treatments induce oxidative stress in prostate cancer cells, leading to cellular damages as well as modulations of cellular signaling including AR signaling.

Effects of oxidative stress on AR signaling

In 2008, oxidative stress was reported to be implicated in AR signaling in prostate cancer (Sharifi *et al.* 2008). SOD2, which regulates ROS levels by converting superoxide to a less reactive species, is reduced by androgen deprivation (Pang *et al.* 2002, Best *et al.* 2005) and is down-regulated in CRPC (Best *et al.* 2005, Quirós *et al.* 2009). Sharifi *et al.* (2008) showed that the suppression of SOD2 induced the activation of AR signaling by ROS production via the following pathways. First, several genes involved in steroid metabolism, including *AKR1C3*, were induced by SOD2 knockdown, and this effect was reversed by the treatment with the antioxidant *N*-acetyl-cysteine (NAC). Changes in the expression of genes related to steroid metabolism can lead to an increase in local *de novo* androgen synthesis in CRPC, thus contributing to castration resistance via AR reactivation (Titus *et al.* 2005). Second, five nuclear receptor co-regulators, including NCOA4 (ARA70), were induced by repressing SOD2 in a ROS-dependent manner. AR reactivation can be induced by altering the balance of such steroid receptor co-regulators (Heemers & Tindall 2007). Lastly, the receptor for interleukin-6 (IL6R) was induced by SOD2 down-regulation, and this effect was reversed by NAC. IL6 activates AR in a STAT3-dependent manner, while antibodies to IL6 reverse castration resistance (Lee *et al.* 2003, Wallner *et al.* 2006). Furthermore, levels of IL6R are predictive of biochemical recurrence of prostate cancer and metastasis (Shariat *et al.* 2001, Kattan *et al.* 2003). Thus, SOD2 repression is found to contribute to castration resistance via AR reactivation by several mechanisms. Inversely, it has been reported that SOD mimetics reduce oxidative stress and exert a suppressive effect on AR expression, including the expression of AR splice variants, and have a therapeutic effect on prostate cancer cells (Thomas & Sharifi 2012). These results suggest that antioxidant therapy is feasible and

promising for the treatment of prostate cancer, including CRPC. We have also independently found that oxidative stress plays a crucial role in AR signaling, leading to the development of CRPC (Shiota *et al.* 2010, 2011a).

Since the findings of Sharifi *et al.* (2008), further evidence supporting a role of oxidative stress in AR signaling has been acquired. AR signaling in CRPC is aberrantly augmented by the low androgen milieu, via various mechanisms including: i) AR overexpression; ii) AR activation by AR co-regulators or intracellular signal transduction pathways; iii) AR mutations or splice variants; and iv) *de novo* androgen synthesis. The effects of oxidative stress on AR signaling are reviewed in the following sections.

AR overexpression

AR overexpression is thought to be one of the major causes of CRPC (Shiota *et al.* 2011b). Many studies have shown that the progression of CRPC is associated with increased AR expression (Gregory *et al.* 1998, Zegarra-Moro *et al.* 2002, Chen *et al.* 2004, Scher & Sawyers 2005), which can be attributed to gene amplification, transcriptional up-regulation, translational up-regulation, and decreased degradation. As we summarized previously (Shiota *et al.* 2011b), various transcription factors activated by oxidative stress, including Twist1 (Shiota *et al.* 2010), YB-1 (Shiota *et al.* 2011c), NF- κ B (Zhang *et al.* 2009), Sp1 (Faber *et al.* 1993, Yuan *et al.* 2005), Myc (Grad *et al.* 1999, Lee *et al.* 2009), CREB (Mizokami *et al.* 1994), and Foxo3a (Yang *et al.* 2005), regulate AR expression. In addition, it has recently been shown that the SREBP-1 transcription factor regulates AR expression (Huang *et al.* 2010), is overexpressed during progression to castration resistance (Ettinger *et al.* 2004), regulates lipogenesis, and induces oxidative stress via NADPH oxidase 5 (Nox5) expression that can be reversed by the Nox inhibitor diphenyliodonium (DPI). Intriguingly, AR expression was shown to be repressed by DPI, indicating that AR expression by SREBP-1 may be mediated by the Nox pathway (Huang *et al.* 2012). Lipogenesis by SREBP-1 may also be involved in AR expression, as our findings demonstrated that statin suppresses AR expression by promoting the degradation of the AR protein (Yokomizo *et al.* 2011).

As described above, several transcription factors regulate AR expression. In addition, the above-mentioned transcription factors may involve the Twist1/YB-1 signaling pathway. NF- κ B (Pham *et al.* 2007) and Sp1 (Ohkuma *et al.* 2007) have been shown

to promote Twist1 transactivation. Myc (Uramoto *et al.* 2002) and Twist1 (Shiota *et al.* 2008a,b, 2009) have been shown to up-regulate YB-1 expression, and YB-1 to increase Twist1 expression via a translational mechanism (Evdokimova *et al.* 2009), suggesting a mutual regulation between Twist1 and YB-1. Taken together, these results indicate that the above-mentioned transcription factors regulate AR expression by mutual interactions, suggesting that Twist1 and YB-1 may be nodal transcription factors in AR expression (Fig. 1).

In addition to transcription factors, other molecules have been reported to be involved in regulating AR expression, likely through intracellular signaling pathways and transcription factors. BLT2 is a receptor for leukotriene B4 and 12-HETE, and plays a critical role in tumor progression, as indicated by the finding that BLT2 is overexpressed in various cancers (Yoo *et al.* 2004, Hennig *et al.* 2008, Choi *et al.* 2010). Recently, it has been reported that a BLT2-linked pathway evokes ROS production and up-regulates AR expression via the Nox4 pathway, while the Nox inhibitor, DPI, reduces AR expression (Lee *et al.* 2012). Furthermore, DPI was shown to reduce cell proliferation in prostate cancer cells, including LNCaP cells which express the mutated AR protein and are dependent on AR for growth, but respond to other steroids than androgens and can be driven to a castration-resistant phenotype. In addition to oxidative stress induced by H₂O₂, cadmium and zinc chloride, which are known to induce oxidative stress, were

Figure 1 Schematic representation of the links between the transcription factors that induce AR expression and promote the development of CRPC. Full colour version of this figure available via <http://dx.doi.org/10.1530/ERC-12-0232>.

reported to increase AR expression in dysplastic glands of rat prostate (Arriazu et al. 2005). The synthetic antimicrobial chemical mequindox was found to induce oxidative stress and AR overexpression in rat testes, indicating a positive connection between oxidative stress and AR expression (Ihsan et al. 2011). These data suggest that oxidative stress induced by internal and external stimuli induces AR overexpression via various cellular processes.

Contrasting reports suggested that inducers of oxidative stress suppress AR expression. The inducer of oxidative stress, *t*-butyl hydroperoxide, suppresses AR expression in H4IIE rat hepatoma cells, indicating that the effect of oxidative stress on AR expression may differ among cell types, and/or may be derived from differences in concentration and/or pharmacological action among oxidants. Additionally, a curcumin analog shown to induce oxidative stress was reported to partially down-regulate AR expression at the transcriptional level, but not by proteasomal degradation (Fajardo et al. 2012). The effect of the curcumin analog was attenuated by the antioxidant NAC, suggesting that AR down-regulation resulted from oxidative stress mediated by the curcumin analog. However, the oxidative stress-inducing effect of the curcumin analog did not appear to be significant. Furthermore, NAC alone down-regulated AR transcript expression, although NAC reduces oxidative stress, which is inconsistent with the authors' proposal that oxidative stress down-regulates AR expression. Similarly, thymoquinone was shown to induce ROS production and down-regulate AR expression (Koka et al. 2010). However, its effect on AR down-regulation was not reversed by NAC, suggesting that either AR down-regulation by thymoquinone induced oxidative stress, or that the effect of thymoquinone on AR expression was independent from its ability to induce oxidative stress.

AR activation by AR co-regulators and intracellular signal transduction pathways

AR co-regulators modulate the transactivation of AR through interactions with AR (Shiota et al. 2011d). Several AR co-regulators, including peroxiredoxin, Hsp27, and EGR-1, have been reported to be activated by oxidative stress, and thus contribute to AR transactivation (Shiota et al. 2011a). In particular, oxidative stress modulates the redox-sensitive molecule peroxiredoxin via its Cys residues. We previously showed that Cys residues in peroxiredoxin are critical in its function as an AR co-regulator (Shiota et al. 2011e), suggesting that

protein modification of AR co-regulators by ROS affects AR signaling.

Several molecules and intracellular signaling pathways play a role in AR transactivation. As previously summarized, cytokines such as insulin-like growth factor, fibroblast growth factor, epidermal growth factor, and IL6 and signal transduction pathways such as mitogen-activated protein kinase, JAK/STAT, protein kinase A, phosphatidylinositol-3-kinase/Akt, and protein kinase C, which may be activated by oxidative stress, can augment AR function (Shiota et al. 2011a). Thus, oxidative stress can activate AR signaling through intracellular signaling pathways that interact with various transcription factors and co-regulators of transcription factors.

AR mutations and splice variants

Although oxidative stress is known to evoke DNA mutations, the implications of oxidative stress-induced mutations of the AR gene are unknown (Khandrika et al. 2009). Mutations in the AR gene may change its ligand binding characteristics or its transcriptional activity, resulting in the modulation of its target gene expression (Brooke et al. 2008, Brooke & Bevan 2009). In addition to AR mutations, several AR splice variants that exhibit transcriptional activity even in the absence of androgen and contribute to the promotion of CRPC have recently been identified (Dehm et al. 2008, Guo et al. 2009, Hu et al. 2009, Sun et al. 2010, Watson et al. 2010). Although a relationship between AR splice variants and oxidative stress has not been reported to date, it is possible that oxidative stress may be implicated in the expression of AR splice variants as it is for splice variants of other genes (Xu & Chu 2007, Soliman et al. 2009, Takeo et al. 2009). Therefore, future studies should examine the effects of oxidative stress-induced mutations of the AR gene or the expression of AR splice variants.

De novo androgen synthesis

De novo synthesis of androgen in adrenal glands and tumors has recently been recognized as a potential cause of CRPC (Stanbrough et al. 2006, Locke et al. 2008, Montgomery et al. 2008), the hypothesis of which was proved by the result of the cytochrome P17 inhibitor abiraterone acetate in a clinical trial (de Bono et al. 2011). Although there is no evidence, at present, that oxidative stress promotes androgen synthesis in prostate cancer, several studies have indicated a relationship between oxidative stress and steroidogenesis. For instance, H₂O₂ has recently been shown to biphasically regulate androgen synthesis in rat Leydig

cells, indicating that oxidative stress within physiological levels promotes steroidogenesis (Zhao *et al.* 2012). These data suggest the possibility that oxidative stress promotes *de novo* androgen synthesis in prostate cancer cells.

Oxidative stress and resistance to androgen deprivation

There is a close relationship between oxidative stress and castration resistance in prostate cancer. Oxidative stress activates AR signaling, which promotes a conversion from androgen-dependent to CRPC through pro-survival and anti-apoptotic roles. We found that H₂O₂-resistant LNCaP cell derivatives of androgen-dependent prostate cancer cells have a high level of AR protein expression and exhibit a castration-resistant phenotype (Shiota *et al.* 2010). In addition, evidence has shown that oxidative stress is increased in CRPC cells, as indicated by higher intracellular ROS levels in castration-resistant LNCaP derivatives, C4-2 cells, compared with LNCaP cells (Shigemura *et al.* 2007), and greater antioxidant protein levels (Kuruma *et al.* 2005, Shiota *et al.* 2011e) and the ability to scavenge ROS (Wu *et al.* 2007) in castration-resistant LNCaP cells and tumors. Thus, AR activation by oxidative stress is thought to render prostate cancer cells resistant to castration.

Pro-survival and anti-apoptotic roles of AR signaling in prostate cancer cells in response to therapeutic interventions other than androgen deprivation

Similarly to castration resistance by the activation of AR signaling, AR signaling may contribute to the survival and anti-apoptotic effects of other insults on cancer cells. Recently, it has been shown that the heart of AR knockout mice is sensitive to oxidative stress induced by doxorubicin (Ikeda *et al.* 2010). Similarly, we have shown that AR knockdown sensitizes bladder cancer cells to doxorubicin (Shiota *et al.* 2012). In addition, AR signaling may be involved in cellular resistance to taxanes including paclitaxel, docetaxel, and cabazitaxel which are key cytotoxic anticancer drugs for prostate cancer, as androgen regulates the expression of the taxane resistance-promoting factor β III-tubulin (Butler *et al.* 2001, Mariani *et al.* 2012). In fact, CRPC cells in which AR was overexpressed developed cross-resistance to taxanes (Kosaka *et al.* 2011). Furthermore, concurrent therapy with paclitaxel and castration was found to improve the suppression of tumor growth and overall survival compared with

sequential therapy with paclitaxel and castration using Shionogi and LNCaP tumor models (Eigl *et al.* 2005). Similarly to these *in vitro* studies, administration of docetaxel plus estramustine in addition to androgen deprivation in a clinical setting was shown to improve a prostate-specific antigen response after 3 months (Fizazi *et al.* 2012). Long-term results and the effects of this treatment regime on overall survival have not yet been obtained. Taken together, these results suggest a favorable outcome from taxane and androgen deprivation combination therapy, and pro-survival and anti-apoptotic roles of AR signaling in response to treatment with taxanes. In addition, androgen and AR expression rendered prostate cancer cells resistant to TGF- β -induced apoptosis (Zhu *et al.* 2008). Similarly, administration of androgen inhibited apoptosis induced by the Akt inhibitor LY294002, while the anti-androgen drug flutamide abolished the anti-apoptotic effect of androgen (Kumar *et al.* 2011). Like cytotoxic agents, radiation cytotoxicity is known to be augmented by the suppression of AR signaling. Numerous lines of evidence have demonstrated that androgen deprivation augments the therapeutic effect of radiation (Granfors *et al.* 1997, Zietman *et al.* 1997, Kaminski *et al.* 2003, Nishiyama 2012). In addition, clinical studies have also shown the favorable effects of castration in combination with radiation on locally advanced prostate cancer with intermediate and high risk (D'Amico *et al.* 2004, 2008, Denham *et al.* 2005, 2011, Jones *et al.* 2011). Interestingly, it has recently been reported that the cell-cycle and DNA repair regulator ataxia telangiectasia-mutated kinase (ATM) contributes to radiation resistance through the up-regulation of AR phosphorylation and activation, which explains the molecular mechanism mediating radiation resistance by AR signaling (Mahajan *et al.* 2012). In fact, where AR signaling was aberrantly activated in CRPC, cells were found to be cross-resistant to

Figure 2 Schematic representation of the pro-survival and anti-apoptotic properties of AR signaling that promote therapeutic resistance to androgen deprivation therapy, chemotherapeutic agents (taxanes), and radiation. Full colour version of this figure available via <http://dx.doi.org/10.1530/ERC-12-0232>.

radiation (Wu *et al.* 2007). Taken together, these findings suggest that AR signaling in prostate cancer cells suppresses the anti-survival and pro-apoptotic effects of various commonly utilized therapeutic cytotoxic and tumor-suppressive interventions, including taxanes or radiation in combination with castration (Fig. 2).

Conclusions and future directions

Oxidative stress can activate AR signaling via the following pathways: i) AR overexpression; and ii) AR activation by AR co-regulators or intracellular signal transduction pathways, thus contributing to the tumorigenesis and progression of prostate cancer, as well as the acquisition of castration resistance. In addition, AR signaling promotes the anti-apoptotic effects and survival of prostate cancer cells in the face of oxidative and cytotoxic stressors, including taxanes and radiation, through the transcriptional modulation of β III-tubulin and ATM. Taken together, AR signaling appears to render prostate cancer cells refractory to various therapeutic interventions such as castration, radiation, and taxanes, indicating that AR is a comprehensive resistance factor and crucial target for prostate cancer treatment. Furthermore, administration of therapeutic interventions such as taxanes and radiation concurrent or before androgen deprivation therapy may exert improved outcome in recurrent or advanced prostate cancer. So far, numerous studies have revealed the usefulness of antioxidants including natural compounds such as vitamin D, vitamin E, carotenoids, lycopene, green tea catechins, and isoflavone, in addition to synthetic antioxidants such as NAC and DPI as a suppressor of AR signaling and prostate cancer growth (Gupta-Elera *et al.* 2012, Huang *et al.* 2012, Shiota *et al.* 2012). Thus, the suppression of AR signaling by antioxidants may be a promising strategy to overcome treatment resistance of prostate cancer, which will be clarified in future.

Declaration of interest

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

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