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Glucocorticoid receptor signaling in breast and prostate cancers: emergence as a therapeutic target

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Abstract

Steroid receptors for androgens and estrogens have essential roles in prostate and breast cancers. Recently, glucocorticoid receptor (GR) activity has also been proposed as having an important role in these cancers. Underscoring the cooperative nature of nuclear receptor activity, data now suggest that GR function in prostate and breast cancers is dependent on the tumor's concomitant androgen or estrogen receptor activity.

Nuclear hormone receptors are part of the larger transcription factor family of nuclear receptors and are defined by their conserved protein structure that includes a ligand-binding domain (LBD), a DNA-binding domain, and N-/C-terminal regulatory domains. After binding to cognate lipophilic ligands, nuclear receptors undergo a conformational change freeing them from chaperone proteins; ligand activation is followed by receptor dimerization, binding to DNA directly or indirectly via associated transcription factors, and subsequently regulating target gene transcription. The nuclear receptor family includes the androgen receptor (AR), glucocorticoid receptor (GR), estrogen receptor (ER), and the progesterone receptor (PR), each of which has a myriad of functions in normal development, human physiology, and disease (1). In development, AR and ER drive luminal epithelial proliferation and differentiation in the prostate and breast, respectively (2, 3). However, in cancer, activation of either receptor can be pro-tumorigenic, and AR/ER antagonists have become effective treatments for prostate and breast cancers (2, 4).

Castration (chemical or surgical) to decrease testicular androgen synthesis is the standard initial therapy for metastatic prostate cancer (PC). Even when PC becomes "castration-resistant" (referred to as CRPC), tumors are often driven by AR signaling and can remain sensitive to potent AR-specific antagonists (5). However, PC resistance to even the most effective anti-AR agents is inevitable. The mechanisms for emergence of resistance to AR signaling blockade are pleiotropic, and likely include androgen-independent, constitutively active AR-initiated signaling (5). There is a profound need to identify targetable resistance mechanisms in refractory CRPC.

Competing interests: R.Z.S and S.D.C and The University of Chicago have a pending patent application with claims related to the use of concomitant glucocorticoid and androgen receptor antagonism in prostate cancer treatment (US patent application no. PCT/US2013/027150). The University of Chicago and S.D.C. have been issued a patent on methods relating to the use of glucocorticoid receptors in breast cancer.

Unlike PC, which is uniformly AR-expressing and almost universally responsive to initial AR pathway inhibition, breast cancer (BC) is subtyped at diagnosis based on the presence or absence of ER expression (6). In ER-negative BC that is resistant to chemotherapy and in ER+ BC that is anti-estrogen refractory, there are clearly heterogeneous mechanisms of tumor escape and progression (7). Here we propose that depending on the AR/ER activation status of a tumor, GR activity can play very different roles in tumor progression.

Glucocorticoid use in the treatment of ER+ breast and AR-active prostate cancers

In normal physiology, GR regulates many genes whose products modulate catabolism, inflammation, and apoptosis/cell survival pathways (1). Synthetic GR agonists, or glucocorticoids (GCs), are often used to treat hematologic malignancies due to GR's ability to induce pro-apoptotic genes, inhibit nuclear factor- κ B, and induce cell cycle arrest (1). In patients with breast, prostate and other non-hematologic cancers, GR agonists are commonly used for their anti-emetic, anti-inflammatory, energy/appetite stimulating properties, and to manage the side effects of chemotherapy (8–10).

Primary BCs are initially subtyped by their ER, PR, and human epidermal growth factor 2 (HER2) expression to guide systemic treatment (11). BCs that lack all three of these proteins are referred to as “triple-negative” (TNBC) and typically relapse earlier than do stage-matched ER+ and/or HER2+ tumors (4). Although TNBCs can be treated with chemotherapy, there are no molecularly defined treatment options for TNBC, and chemotherapy response is often limited (11). Clinically, GCs are used in conjunction with BC chemotherapy to mitigate allergic reactions (10). Studies have shown mixed effects of GC use on patient survival, with modest effects of GCs as a single agent and no effect when used in combination with other drugs (12). Pre-clinically, GR activation may reduce estrogen-induced proliferation in ER+ BC, but the use of GCs and anti-estrogens as a combination treatment in BC has not shown a significant benefit (13).

In PC, metastatic tumors eventually progress to CRPC despite androgen deprivation but often remain AR driven, as evidenced by clinical efficacy of more potent AR-directed therapies. There are several standard options for the treatment of CRPC, including chemotherapies (docetaxel/cabazitaxel), immune based therapy (sipuleucel-T), potent AR-targeted therapies (abiraterone acetate, enzalutamide), and intravenous radionuclide (Radium-223 dichloride). GCs have been used in CRPC as single agents and are commonly used in combination with chemotherapy and abiraterone acetate. As a single agent, GC treatment in CRPC can improve the quality of life and also decrease PSA, a PC-specific serum tumor marker encoded by an AR target gene, in approximately 10–25% of patients (9, 14, 15). GR overexpression is sufficient to decrease AR-expressing PC cell line proliferation *in vitro* (16). Furthermore, ligand-activated GR attenuates androgen-activated AR gene expression, suggesting an AR- dependent mechanism through which GR could act as a tumor suppressor in prostate cancer (17). Thus, laboratory and clinical evidence suggest that, similar to ER+ BC, when AR is present and remains active, GR activity can inhibit tumor cell growth [Figure 1A].

It should be noted that the therapeutic contribution of GCs in BC and PC in combination with other active therapies is not known (9, 12, 14, 15). Furthermore, there is emerging evidence that the molecular actions of GCs and the role of the GR may shift from an anti-proliferative to a pro-cell survival role when ER is absent in BC or AR is blocked in PC (18–20). This context dependency of GR function with respect to ER or AR activity is discussed below.

Complexity of GR expression and activity in breast cancer

The role of GR in BC tumor biology appears to depend on the context of ER expression: in BC patients with early-stage ER+ tumors, high tumor GR expression is associated with a longer time to relapse (better prognosis) both in patients who do not receive adjuvant therapy and in tamoxifen (a selective ER modulator) -treated patients [Figure 1A] (20). This may be a result of GR's role in modulating expression of poor prognosis and/or good prognosis ER transcriptional targets (21). Conversely in ER-negative BC including TNBC, high tumor GR expression correlates with a decrease in time to relapse (worse prognosis) for both chemotherapy-naïve and chemotherapy-treated early-stage patients, suggesting a role for GR in tumor aggressiveness and in resistance to chemotherapy [Figure 1B and C] (20). Taken together, these results suggest that GR's function is altered by crosstalk with ER in ER+ BC, which is absent in TNBC. This notion is supported by laboratory data showing that GR activation diminishes chemotherapy efficacy and apoptosis in TNBC xenograft tumors (22), and that systemic treatment with a GR antagonist reverses these effects (23). Because early-stage TNBCs with very high GR expression (approximately 25% of TNBC) have a far worse prognosis than TNBC/GR-low tumors, GR expression may also serve as a prognostic biomarker in TNBC (20). Furthermore, GR expression is expected to predict the usefulness of GR antagonist therapy in conjunction with chemotherapy in otherwise chemotherapy-resistant TNBC. This concept is being tested in ongoing TNBC Phase 1 clinical trials that include evaluation of tumor tissue for GR expression and the use of the GR antagonist mifepristone in conjunction with conventional chemotherapy [NCT 02046421].

In the absence of ER activity, GR-mediated gene expression of pro-survival genes such as serum/glucocorticoid regulated kinase 1 (*SGK1*) and mitogen activated protein kinase phosphatase 1 (*MKPI*) appears required for GR effects (23). In the presence of ER, GR may be primarily affecting ER activity. For example, GR appears to modify chromatin accessibility for ER and vice-versa (24). Alternatively, GR may antagonize ER-mediated gene expression by interfering with ER binding to DNA (13). Furthermore, PR effects on ER-mediated growth may be influenced by GR signaling (25). Although this article does not focus on PR or its effects, an important point to consider is that nuclear hormone receptor cross-talk is dynamic and that all nuclear hormone receptors are likely dependent on each other for their actions. A greater understanding of the role of GR activity in the absence or presence of ER activation will be important to fully understand the role of GR in breast cancer subtypes.

GR signaling as a tumor cell survival pathway in AR-antagonized CRPC

As in BC, where GR expression and activity may depend on ER activity, GR activity in prostate cancer may differ depending on AR activation status. GR shares many similarities with AR: structural similarity, identical or near identical consensus DNA-binding motifs, and regulation of a subset of overlapping genes (17, 26). Although GR activation can be anti-proliferative when AR signaling is intact as discussed above, AR and GR similarities suggest the possibility that in the context of a fully antagonized AR, increased GR expression and activity in PC may become a bypass cell survival mechanism.

The recent recognition of a substantial overlap between AR/GR regulated genes in PC, including many genes traditionally considered to be AR-specific, is consistent with the hypothesis that after potent AR inhibition, GR activation might “evolve” to promote PC growth (17). This hypothesis provides one possible mechanism for GR-mediated CRPC growth after potent AR antagonism (18, 19). Although GR expression is low in primary prostate cancer and may actually be lower than in benign prostatic hyperplasia, GR expression increases in PC after exposure to systemic AR inhibition (18, 27–29); this observation is supported by laboratory models finding that GR expression increases in PC cell lines and xenografts after anti-AR signaling conditions (18, 19). Furthermore, a direct relationship between the two receptors is supported by recent data demonstrating that AR directly represses GR expression, providing a potential mechanism for increased GR expression in the presence of AR blockade (28). There is also clinical evidence supporting the hypothesis that increased tumor GR activity promotes CRPC progression despite AR antagonist therapy: patients whose bone metastases expressed relatively high GR after treatment with the AR antagonist, enzalutamide, were less likely to derive long-term benefit from enzalutamide (18). Pre-clinically, activation of GR can diminish the efficacy of AR inhibition and accelerate castration and enzalutamide resistance, whereas in CRPC model systems GR antagonism improves sensitivity to AR inhibition (18, 19). GR antagonists may therefore help block compensatory GR-mediated pro- tumor cell survival activity. However, anti-GR therapies may not be effective as single agent therapies in CRPC because, as mentioned above, single-agent glucocorticoids can have tumor-suppressive properties, potentially through modulation of AR activity; therefore if AR is not blocked simultaneously, this could contribute to CRPC progression.

After AR antagonism in PC, tumor GR transcriptional activation may impart resistance to therapy via activation of cell survival mechanisms (as in TNBC). Subsequent to AR blockade, active GR may substitute for antagonized AR by inducing anti-apoptotic target genes such as *serum/glucocorticoid regulated-kinase 1 (SGK1)* (18, 19). In CRPC model systems, SGK1 antagonism is sufficient to reverse GC-mediated resistance to androgen-directed therapy (19). Thus, blockade of downstream pro-survival target gene products (rather than systemic GR antagonism) is also a potential strategy to overcome CRPC progression. These data suggest that tumor GR activity may be a targetable driver of resistance along with AR antagonism therapy in CRPC.

Translational challenges and opportunities

Data supporting a role for GR activity in promoting breast and prostate cancer progression are accumulating, and a number of translational questions are emerging. Cancer is a complex, heterogeneous disease with numerous effector pathways responsible for progression. Consequently, there is great need for predictive biomarkers that will allow for precise and individualized treatments. Because cancer clearly adapts under therapeutic pressure, there may be a need for iterative biopsies and tissue acquisition to determine the proper course of treatment. In PC, GR expression can increase after AR blockade; therefore a biopsy might be necessary before and after initiation of enzalutamide treatment to assess for increased GR expression and to select those patients most likely to benefit from GR antagonism (18, 19, 27). Similarly, in breast cancer, there may be selection for GR-high, chemotherapy-resistant TNBC cell populations over the course of standard chemotherapy (23). Because of the difficulty associated with serial biopsies, alternative sources of patient-derived tumor specimens, such as circulating tumor cells (CTCs), could enhance translational efforts. Although there are a myriad of CTC technologies, a method that allows for quantification of nuclear hormone receptor expression and cellular localization would be ideal (30).

Targeting GR systemically in advanced breast and prostate cancers presents several challenges. In PC, GR-directed therapies will likely be needed continuously to block endogenous GCs, and it is unknown if long-term GR blockade will be safe or tolerable. Mifepristone, the only FDA-approved GR antagonist, has many potential drug-drug interactions and will likely interfere with enzalutamide's metabolism, making development of such a combination challenging. These questions are currently being addressed in a phase I/II trial of mifepristone and enzalutamide (NCT 02012296). In BC, mifepristone is being studied in conjunction with chemotherapy for GR+ metastatic TNBC. Similar pharmacokinetic and possible pharmacodynamic considerations are being addressed in TNBC trials with mifepristone and various chemotherapies (NCT 02014337, NCT 02046421).

The development of more tissue-selective GR antagonists, similar to the selective estrogen-receptor modulators used in the treatment of BC might address potential issues with systemic GR inhibition. Newer non-steroidal and more selective GR modulators could achieve tissue-specific modulation and reduce drug-drug interactions. Another layer of complexity in fully understanding the role of GCs and GR in these cancers involves the potential effects that GCs may have on other (non-GR) nuclear hormone receptors. For example, under the selective pressure of AR antagonism, one may observe AR mutations that allow AR activation by cortisol and thereby enable CRPC cell survival (31). In this case, a selective GR antagonist would likely be ineffective in mitigating the GC effect on PC growth.

Conclusions

In breast and prostate cancer, effects of GR activity on tumor cell biology are dependent on concomitant ER and AR activity. Several recent papers have pointed to an ER context-

dependent role for the GR in BC, and similarly there appears to be an AR context-dependent role for GR in PC biology (18–20, 23). The context dependency of GR function [Figure 1] is consistent with the concept that nuclear receptors can modify each other's activity. Understanding GR signaling in a context-dependent manner will allow GR-directed therapy to be used most appropriately. As a new generation of more selective GR antagonists becomes available, decreased drug-drug interactions and increased GR specificity are expected. Regulation and function of tumor GR in the natural history of tumor development, including identifying downstream GR target genes, understanding GR's chromatin remodeling ability, and characterizing dynamic interactions with other nuclear hormone receptors, coactivators, and repressors will be explored (13, 18, 19, 32–34). A better understanding of GR-regulated resistance to cytotoxicity may reveal other targetable pathways. For example, the GR target gene *SGK1* has been identified as a critical mediator of therapy resistance in both PC, in the context of AR antagonism, and in BC. Although much remains to be understood about effectively using GR-directed therapies, recent studies of GR function in breast and prostate cancer model systems with variable AR and ER activity are yielding surprising and conceptually congruent results.

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Figure 1. Context-dependent function of GR

GR function differs and is predicted to depend upon the context of estrogen receptor (ER) expression (breast cancer) or androgen receptor (AR) activity (CRPC, castration-resistant prostate cancer). **A)** When ER (breast) or AR (CRPC) is expressed and active, concomitant GR activation results in a growth-suppressive and anti-proliferative phenotype, presumably because of cross-talk between GR and ER or AR; **B)** in TNBC treated with chemo or CRPC treated with effective AR antagonism, tumor cells with low GR expression (GR-) are susceptible to cytotoxic/antiproliferative effects of chemotherapy or AR signaling blockade; **C)** however, in TNBC or AR-antagonized CRPC, higher GR expression and activity (GR+++) mitigates therapy effectiveness, presumably due to altered GR function in the absence of ER expression or loss of AR function.