Mini-Review

The Nexus of Endocrine Signaling and Cancer: How Steroid Hormones Influence Genomic Stability

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Abbreviations: ADT, androgen deprivation therapy; AR, androgen receptor; ATR, Rad3-related; CDK, cyclin dependent kinase; DDR, DNA damage response; DSB, double-stranded break; E2, estradiol; ERα, estrogen receptor alpha; IR, ionizing radiation; MDC1, Mediator of DNA Damage Checkpoint 1; MPG, 3-methyladenine DNA glycosylase; NHEJ, nonhomologous end-joining; PARP, poly(ADP-ribose) polymerase; PCa, prostate adenocarcinoma; PR, progesterone receptor; RT, radiotherapy; TOP2B, topoisomerase II beta.

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Abstract

Endocrine-driven malignancies, including breast and prostate cancer, are among the most common human cancers. The relationship between sex steroid hormones (eg, androgen, estrogen, and progesterone), their cognate receptors, and genomic stability lie at the center of endocrine-driven cancer development, progression, and therapeutic resistance. A variety of direct and indirect mechanisms have been described that link steroid hormone signaling to the loss of genomic integrity that drives early carcinogenesis. These effects are often enriched within endocrine receptor cistromes, accounting for the high proportion of mutations and rearrangements in the region of hormone response elements. In other cases, the effects are generalized and rely on a complex array of genetic, epigenetic, and metabolic interactions. Both androgen and estrogen receptors directly modulate the DNA damage response by trans-activating DNA damage response genes and redirecting the cellular repair machinery in the wake of genotoxic stress. Here we review the key mechanistic underpinnings of the relationship between sex steroid hormone receptors and genomic stability. In addition, we summarize emerging research in this area and discuss important implications for cancer prevention and treatment.

Keywords: Endocrine cancer, steroid hormones, prostate cancer, breast cancer, androgen receptor, estrogen receptor, genomic stability

Steroid hormones, including corticosteroids and sex steroids, are essential for homeostatic control of vital systems including metabolism, immune function, stress response, fluid balance, and development. Perturbation of canonical hormone signaling leads to a broad array of disease states and can drive cancer-related phenotypes at the cellular
level, including proliferation, migration, invasion, and metastases (1, 2). In recent years it has become increasingly clear that steroid hormone signaling has both direct and indirect influence over the stability of the genome, and therefore on cancer initiation and progression. Steroid hormone signaling alters genomic stability via several mechanisms, including increased oxidative stress (3-8), induction of DNA double-stranded breaks (DSBs), enhancement of DNA-protein adduct formation (9), and initiation of gene rearrangement events (10-13). To counteract these effects, endocrine-directed therapies have emerged as chemopreventive and therapeutic agents for a variety of common cancers, notably breast and prostate cancer (1, 14). Increasingly, contemporary hormone receptor-targeted therapies are used in conjunction with genotoxic stresses (1, 2). In recent years it has become increasingly evident that ADT and RT (26, 27), as well as ADT and chemotheraphy, underscore the importance of understanding the complex relationship between hormone receptor activity and genomic stability (15-23). In this review, we explore the mechanistic underpinnings of the relationship between steroid hormone signaling, genomic stability, and the DNA damage response and discuss its therapeutic implications.

Androgen Receptor Signaling and Genomic Stability in Prostate Cancer

Androgens, estrogens, and progestins collectively make up the class of steroid hormones known as sex steroids. The cellular target of androgens (eg, testosterone and dihydrotestosterone) is the androgen receptor (AR), which binds intracellular androgens, dimerizes, translocates to the nucleus, and activates transcription of androgen response genes. The AR is well-established as a critical driver of prostate adenocarcinoma (PCa) and the AR pathway represents an essential therapeutic target in this disease. Androgen deprivation therapy (ADT) remains the first-line treatment for advanced PCa (24, 25) and the combination of ADT and radiotherapy (RT) is a standard for locally advanced high-risk PCa. Multiple randomized prospective trials have confirmed a substantial cooperative effect between ADT and RT (26, 27), as well as between ADT and chemotherapy, leading to a significant improvement in survival with combined treatments (28-33).

A principal mechanism driving this cooperativity was established in studies showing that AR directly transactivates DNA damage response (DDR) genes (34, 35), which in turn drive resistance to DNA-damaging therapies. It was observed that suppressing androgen signaling led to an increased accumulation of DNA damage in the wake of genotoxic stress. Conversely, supplementing androgen-depleted cells with a synthetic androgen upregulated the DDR, resulting in more efficient DNA repair and increased cancer cell survival following ionizing radiation (IR) (34). This observation was directly tied to AR’s binding in upstream cis-regulatory elements of DDR genes, including PRKDc, which encodes the DNA-dependent protein kinase catalytic subunit (DNA-PKcs). PRKDc is a critical factor required for nonhomologous end-joining (NHEJ) repair and its expression is tightly correlated with sensitivity to IR (34). Follow-up work examining the gene expression profiles of human castrate-resistant prostate cancer models treated with the second-generation anti-androgen drug apalutamide (ARN-509) pinpointed a subset of 32 DDR genes containing functional AR binding sites, mainly in enhancer elements (35). These studies again confirmed that androgen deprivation impaired resolution of ionizing radiation-induced DNA DSBs and demonstrated that the repair was primarily attributable to diminished classical NHEJ (Fig. 1, left panel).

A teleologic explanation for the coordinate activity of AR and DNA repair machinery emerges from the observation that androgen signaling creates physiologic DNA DSBs, a requirement for efficient gene transcription. Intrinsic androgen signaling in prostate cells involves the co-recruitment of AR and topoisomerase II beta (TOP2B) to the promoter of proximal androgen response elements. TOP2B mediated DSBs are known to occur at an increased frequency in the regulatory regions of AR target genes. (13) In early neoplastic and preneoplastic prostate cells, androgen-induced TOP2B mediated DSBs are recombinogenic and lead to de novo production of characteristic rearrangements such as TMPRSS2-ERG fusions in a TOP2B-dependent manner. These androgen-induced TOP2B-dependent DSBs participate in a variety of common genomic recombination events that likely drive the progression of early prostate cancer.(13) Whole-genome sequencing has identified rearrangements belonging to the ETS protein family ETV1, ETV4, and ETV5 at a high frequency in PCa (38-41). ETS rearrangements, for example, TMPRSS2-ERG, occur in nearly half of prostate cancers, resulting in the activation ERG fusion oncogenes (12, 42). Interestingly, the TMPRSS2-ERG gene fusion product blocks XRCC4-mediated NHEJ repair and sensitizes prostate cancer cells to poly(ADP-ribose) polymerase (PARP) inhibition (43, 44). Cistrome partitioning of the genome reveal enrichment of noncoding somatic single nucleotide variants in prostate tumor cistromes of master transcription regulators, including AR. (45) Large-scale
whole-genome sequencing data confirm TF binding affects somatic mutation distribution in PCa (46). In particular, AR binding causes an enrichment in regional somatic alterations surrounding AR binding sites and the pattern of persistent regional mutations that result impaired repair of abasic sites in AR/transcription factor–bound DNA (47). A parallel phenomenon has been observed at ER binding sites in breast cancer, supporting the idea of a destabilizing class effect of nuclear hormone receptors.

Nuclear hormone receptor signaling also plays an indirect role in promoting genomic instability through dysregulation of the cell cycle. Prostate epithelial cells deprived of androgen exit the cell cycle and arrest in G0 (48-50). Expression of D-type cyclins (cyclins D1 and D3) is suppressed in ADT-responsive prostate cancer cells after steroid deprivation and contributes to cell cycle arrest (50, 51). Conversely, androgen stimulation induced mTOR-dependent translation of D-cyclins, resulting in activation of cdk4/6 (51). D-cyclin mRNA levels were unchanged by ADT in prostate cancer cells, which is distinct from what is observed in breast cancer cells (52, 53). Thus, AR regulates early G1 entry primarily through translational control of D-type cyclins. AR is also reported to directly bind to DNA replication factor Cdc 6 and regulate the S phase of the cell cycle (54, 55). By obscuring the G0/G1 and G1-S checkpoints, AR signaling augments vulnerability to intrinsic and extrinsic genotoxic stressors, further driving genomic instability. These intrinsic destabilizing forces combine with exogenous genotoxic stress, and metabolic dysregulation, such as activation-induced cytidine deaminase and LINE-1 repeat-encoded ORF2 endonuclease, to establish the complex array of genomic alterations that drive prostate cancers (10).

**Estrogen/Progesterone Signaling and Genomic Stability in Breast Cancer**

Estrogens and progesterone are sex steroids which, similarly to androgens, have been implicated in carcinogenesis (14, 56). Estrogen receptor alpha (ERα) plays an important role in a variety of cancers, notably breast, uterine, and
ovarian carcinoma. When bound to its ligand, estradiol (E2), it drives survival, proliferation, and influences genomic stability. Anti-estrogen therapy is an important component of treatment for ERα expressing breast cancer. Similarly, progesterone receptor (PR) is a ligand-activated hormone receptor that has 2 common isoforms (A and B). The isoforms can act as heterodimers or homodimers, which bind DNA at progesterone response elements to transactivate target genes (57). ER and PR have been implicated in both the maintenance and disruption of genomic integrity through several mechanisms.

One of the first links between ERα and DNA damage repair was discovered when an interaction between ERα and the DNA repair protein 3-methyladenine DNA glycosylase (MPG) was identified (58). Through in vitro pull-down assays, a direct interaction was demonstrated between ERα and MPG via the DNA and ligand-binding domains, respectively. ERα increased MPG acetylation and enhanced MPG-catalyzed removal of mismodeled hypoxanthine from DNA (58). The Mediator of DNA Damage Checkpoint 1 (MDC1), now recognized as part of the ERα co-activator complex, was initially found to interact with γH2AX, serving to recruit the MRN complex (MRE11/RAD50/NBS1) to sites of DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62). Cells lacking MDC1 are sensitive to IR, in part due to DNA DSBs and initiating both NHEJ and HR (59-62).

Similar to AR in prostate cancer, E2 exposure in Erα-expressing breast cancer cells results in increased γH2AX foci formation. These H2AX foci require transcriptionally competent ERα and the catalytic activity of TOP2B and occur at the promoters of the E2 inducible genes (eg, TFF1) (63). Several functionally comprehensive studies initially implicated transient ERα activation and TOP2B in mediating dsDNA break formation during breast cancer pathogenesis. It was shown that TOP2B-mediated DSBs result in activation of PARP-1 enzymatic function, in turn driving a nucleosome-specific histone H1-HMGB exchange (64). This work first illustrated a recurrent theme in nuclear hormone receptor–driven genomic instability; specifically, a mechanistic link between TOP2B-dependent dsDNA breaks and components of the DNA damage and repair machinery during hormone-regulated gene transcription. E2/ERα also plays an important extranuclear role in cyclin D1 dependent DDR in human breast cancer cells. The E2-induced DDR requires extranuclear cyclin D1, which binds ERα at the cytoplasmic membrane and augments AKT phosphorylation (Ser473), driving a cascade that leads to increased intra-nuclear γH2AX foci formation, cyclin D1 recruitment by E2, and the stabilization of RAD51 (a gene necessary for homologous recombination repair). Augmentation of Akt1 phosphorylation by E2 contributes to an aberrant growth signaling and cyclin D1 dependent homolog-directed DNA repair, highlighting an important link between ER and DDR (65). In ER-positive breast cancer cells, E2 blocks ataxia telangiectasia-mutated (ATM) and Rad3-related (ATR) activity via plasma membrane-associated ERα (66). E2 delayed the assembly and prolonged the resolution of γH2AX and RAD51 nuclear foci. This finding helped to establish ER as a critical mediator of the ATR cascade required for an efficient DDR in breast cancer cells (65). The cumulative effect of ER signaling on genomic stability is complex and context-specific. For example, while ER signaling upregulates DDR in some contexts, its activity has also been linked to TOP2B mediated break formation in regulatory regions of ER target genes (64).

Progesterone receptor (PR) is highly specific for its ligand, progesterone, and the active form binds to progesterone response elements to initiate target gene transcription (67). A major factor that regulates PR levels in a variety of cells and tissues is 17β-estradiol or related estrogens bound to ER. In human breast cancer cells, the promoters controlling PR transcription contain estrogen response elements recognized by ER and its cofactors (68, 69). PARP1, known to have a role in DNA damage repair and the maintenance of genomic integrity, is one such nuclear enzyme-linked to PR (70, 71). The DNA-PK subunit Ku70, an early component of NHEJ repair, also interacts with PR in a complex that contains PARP-1. PR transcriptional activation is modulated by DNA-PK, which auto-phosphorylates and subsequently phosphorylates PR (70).

Cyclin-dependent kinase 2 (CDK2) activation has also been demonstrated following progestin treatment in breast cancer cells. Activated CDK2 phosphorylates downstream targets including PARP-1, increasing its enzymatic activity. Conversely, activation of PARP-1 via CDK2 is required to initiate the PR transcriptional program, establishing positive feedback loop (72). PR is not only an ERα target gene, but also an ERα-associated protein (73). In the presence of their respective agonists, PR associates with ERα to direct ERα-chromatin binding events in breast cancer cells. Therefore, ER and PR are capable of acting cooperatively to modulate effects on the DNA repair machinery and directly modulate the genomic stability of breast cancer cells.

**Targeting Sex Steroids in Combinatorial Treatment Strategies**

DNA-damaging therapies including RT and chemotherapy remain a cornerstone of cancer care. Concerning RT, technical advances such as image-guided RT or intensity-modulated RT have led to the enhancement of the
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therapeutic ratio (74). RT-induced cell death is primarily a consequence of unrepaired DNA damage, especially DSBs (75, 76), which lead to chromatin destabilization and mitotic catastrophe. While an established hallmark of cancer is relative vulnerability to DNA damage (77, 78), tumor cells with highly efficient DNA repair manifest a radioresistant phenotype (79), whereas deficiencies in DSB repair pathways sensitize to IR (80). DNA lesions induced by RT activate the DDR by initiating a cascade of posttranslational modifications that activate downstream signaling pathways (81). DSBs are the most lethal lesions and even a single unrepaired DSB can trigger cell death (76). Therefore, treatments that even modestly inhibit the DNA repair machinery (ideally selectively in cancer cells) have the potential to dramatically enhance therapeutic efficacy (82, 83). Targeting the dysregulated steroid hormone signaling axes in neoplastic tissues in combination with IR or chemotherapy offers an opportunity to selectively target endocrine-driven tumors with relative sparing of normal tissues (82, 84-86).

Hormonal therapy for PCa diminishes circulating gonadal androgens via suppression of the hypothalamic-pituitary-gonadal axis (LHRH analogs) and/or targets androgen receptors using competitive antagonists (antiandrogens) (17). The first attempts to combine hormonal therapy with RT were made using Shinogi murine models (with implanted PCa) (87). The study showed that hormonal therapy allows for a significant reduction in the RT dose required to eliminate 50% of tumors (TCD50—the dose required for 50% tumor control). The greatest combinatorial efficacy was observed when hormonal therapy was used before a series of exposures to radiation (neoadjuvant therapy) (87). Another study, using a Dunning rat PC model, compared the efficacy of RT in combination with 1) hormonal therapy used 14 days prior to RT; 2) hormonal therapy during RT; and 3) hormonal therapy used 14 days after RT. The maximal therapeutic effect was achieved with RT + neoadjuvant HT, confirming the results of the previous study (88). While these results show that sustained hormone suppression sensitizes cells to RT, acute androgen stimulation paradoxically further sensitizes cells to IR. An appropriately timed dose of androgens (approximately 6 hours prior to RT) can increase tumor cell death following IR and reduce prostate cancer cell survival by inducing increased DNA DSB formation (89).

In breast cancer, selective estrogen receptor modulators (SERMs) and aromatase inhibitors are the mainstays of hormonal adjuvant treatment. Adjuvant and long-term maintenance tamoxifen is associated with a significant reduction in breast cancer recurrence and improved overall survival (90). Similarly, aromatase inhibitors provide a disease-free survival benefit in postmenopausal women (91). Compared with radiation alone, the combination of radiation and letrozole produced a significant shift in cell cycle distribution which had the effect of sensitizing the cells to appropriately timed doses of radiation (92). However, in the clinical setting, retrospective studies to date have shown no difference in disease-free survival between concurrent versus sequential use of aromatase inhibitors along

| Hormone Receptor | Molecular Partner | Mechanism | Disease Relevance | Reference |
|------------------|-------------------|-----------|-------------------|-----------|
| Androgen Receptor | TOP2B | DSB formation during transcriptional activation | Prostate Cancer | Haffner et al., Nat Gen. (2010) |
| Androgen Receptor | PRKDC | Binding to cis-regulatory element of PRKDC | Prostate Cancer | Goodwin et al., Cancer Discov. (2013) |
| Androgen Receptor | DDR genes | Binding to enhancer elements of 32 DDR genes | Prostate Cancer | Polkinghorn et al., Cancer Discov. (2013) |
| Androgen Receptor | Ku70 | NHEJ | Prostate Cancer | Mayeur et al., J Biol Chem. (2005); Al-Ubaidi et al., Clin Cancer Res. (2013) |
| Androgen Receptor | Cdc 6 | Regulate the S phase of cell cycle | Prostate Cancer | Jin et al., Nucleic Acids Res. (2009) |
| Estrogen Receptor | MDC1 | Recruiting the MRN complex initiating both NHEJ and homologous repair | Breast cancer | Stewart et al., Nature (2003); Lou et al., Mol Cell. (2006); Lamarche et al., FEBS Lett. (2010); Zhou et al., Intl J Biol Sci. (2015) |

| 17-beta-estradiol (E2) | ATM | Delayed the assembly and prolonged the resolution of γH2AX and RAD51 nuclear foci | Breast cancer | Pedram et al., Mol Biol Cell. (2009) |

Abbreviations: ATM, ataxia telangiectasia-mutated; ATR, Rad3-related; DDR, DNA damage response; DSB, double-stranded break; MDC1, Mediator of DNA Damage Checkpoint 1; NHEJ, nonhomologous end-joining; TOP2B, topoisomerase II beta.
with radiation therapy (93). Similar to letrozole treatment, tamoxifen showed radiosensitization properties in vitro (94); however, no difference was observed in survival or locoregional recurrence between concurrent versus sequential use of adjuvant tamoxifen in clinical studies (95-97).

Clinical trials investigating novel combinations of targeted endocrine agents with conventional antineoplastic therapies are ongoing and will ultimately shed further light on the complex interplay between hormone receptor biology and genomic stability in patients.

**Conclusion**

Steroid hormones modulate genomic stability in complex, context-dependent networks which in turn play a fundamental role in endocrine-driven cancer development and progression (Table 1). Efforts to characterize the relationship between the DDR and endocrine signaling have led to more effective endocrine therapy combinations. AR, an established driver of PCa, is a direct transactivator of DDR genes that mediate resistance to conventional therapies including chemotherapy and radiation. This observation explains the marked synergy between ADT and radiotherapy in primary prostate cancer. Similarly, the ER and PR modulate essential cell cycle checkpoints and repair mechanisms (eg, NHEJ) to promote breast, ovarian, and endometrial carcinogenesis. As new endocrine therapies emerge, efforts to characterize their effects on hormone receptor–driven genome instability and DNA damage will be important in guiding their clinical application, minimizing resistance, and maximizing treatment efficacy.

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