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Linking DNA damage and hormone signaling pathways in cancer

Matthew J. Schiewer^{1,2} and Karen E. Knudsen^{1,2,3,4,*}

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Abstract

DNA damage response and repair (DDR) is a tightly controlled process that serves as a barrier to tumorigenesis. Consequently, DDR is frequently altered in human malignancy, and can be exploited for therapeutic gain either through molecularly targeted therapies, or as a consequence of therapeutic agents that induce genotoxic stress. In select tumor types, steroid hormones and cognate receptors serve as major drivers of tumor development/progression, and as such are frequently targets of therapeutic intervention. Recent evidence suggests the existence of crosstalk mechanisms linking the DDR machinery and hormone signaling pathways that cooperate to influence both cancer progression and therapeutic response. These underlying mechanisms and their implications for cancer management will be discussed.

Keywords

cancer; hormones; DNA repair; transcription; nuclear receptor

STEROID HORMONES AND DNA REPAIR

Steroid hormones are systemically circulating small molecules that elicit autocrine, paracrine, and endocrine functions in physiology and pathology, most often through the binding to and regulation of cognate nuclear receptor (NR) [1]. Steroid hormones influence distinct and important cancer-associated phenotypes, including but not limited to proliferation, apoptosis, migration, and invasion [2]. Steroid-induced biological outcomes occur in a context-dependent manner in multiple malignancies, including breast (BrCa) [3] and prostate (PCa) cancers [4]. As such, therapy for selected hormone-dependent cancers focuses on diminishing availability of ligand or direct antagonism of NRs.

*To Whom Correspondence Should Be Addressed: Karen E. Knudsen, Ph.D., Departments of Cancer Biology, Urology, & Radiation Oncology, Thomas Jefferson University, Kimmel Cancer Center, 233 10th St., BLSB 1008, Philadelphia, PA 19107, tel: +1 215-503-8574 (office), +1 215-503-8573 (lab), karen.knudsen@jefferson.edu.

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While the biological implication remains uncertain, steroid hormones (e.g. estrogens, androgens, glucocorticoids) have also been associated with induction of genotoxic stress via multiple mechanisms, such as formation of DNA adducts, or generation of reactive oxygen species (ROS) [5–14]. These effects can be exacerbated by both genetic aberrations, such as through mutation of important DNA repair genes, as well as chemical perturbations [15–17], or through use of nuclear receptor antagonists. Conflicting data exists as to whether hormones are carcinogenic or cancer-protective [18], and the discrepancies are context-, model-, and hormone-specific. However, steroid hormones have been selectively shown to promote transformation [19, 20], as well as generate complex genomic rearrangements through induction of double-strand breaks (DSBs) that are associated with tumorigenesis [21–24]. Conversely, hormone signaling has also been shown to stabilize DNA [25, 26] and be chemopreventive [27], thus obfuscating the ability to generalize the effects of any one NR on genome stability. Additionally, some NR antagonists (e.g. tamoxifen) have also been demonstrated to induce DNA damage [28, 29], adding further complexity.

DDR pathways are complex, highly regulated biological processes that protect the genome from both low-level DNA damage induced by DNA replication and other metabolic processes, as well as from exogenous DNA damage. DDR encompasses a number of parallel and intersecting pathways that serve as checkpoints for replication in order to repair single-strand breaks (SSBs) through base excision repair (BER), double-strand breaks (DSBs) via either homologous recombination (HR) or nonhomologous end-joining (NHEJ), bulky DNA adducts via nucleotide excision repair (NER), and mismatches/insertions-deletions via mismatch repair (MMR). The mechanisms and pathways governing DDR have been reviewed previously [30–35]. Alterations in the DDR machinery increase cancer susceptibility by creating a permissive state for potentially transforming mutations, and cell death, due to an inability to control damage. As such, understanding how DDR contributes to carcinogenesis and how DDR may be targeted for therapeutic benefit in cancer is an expansive and necessary field of study.

Evidence has emerged demonstrating that multiple functions of NRs are influenced both by DNA damage as well as components of the DDR machinery. Conversely, NRs also influence DDR gene expression and function. This interplay between NR and the DDR machinery has potentially strong tissue- and hormone-dependent implications for hormone-sensitive malignancies. This review will explore the bidirectional cross talk between hormones/NRs and the DDR machinery, and the clinical implications thereof.

HORMONAL REGULATION OF UPSTREAM DNA DAMAGE SIGNALING

The tumor suppressor p53 (*TP53*) gene encodes p53, which is the most mutated gene in human malignancies. p53 is considered the “guardian of the genome”, sensing DNA damage and other abnormalities, and serving as a decision point for DNA repair or apoptosis [36]. Estrogen and progesterone signaling have been reported to activate the p53 axis in three distinct ways: (1) directly via activation of the estrogen receptor alpha (ER α) and increased *TP53* mRNA expression [37], (2) by estrogens serving a rheostat function to modulate both p53 levels and activity [38], or (3) combined estrogen/progesterone treatment resulting in activation of p53 function [39]. The downstream biological effects of an estrogen/

progesterone combination include decreased proliferation, increased apoptosis, and reduced tumor formation in a *Trp53* heterozygous murine mammary model [39]. In sum, estrogen and progesterone signaling promote the activity of p53, indicating that female sex hormones have the potential to positively regulate tumor suppressor function.

Conversely, male sex hormones have been implicated in diminishing p53 function. Androgen signaling through the androgen receptor (AR) inhibits p53 function in models of hepatocellular carcinoma (HCC) [40], leading to reduced apoptosis and increased proliferation. It has been reported that dexamethasone (a glucocorticoid receptor agonist) treatment when in combination with the chemotherapy drug cisplatin (CDDP) reduces efficacy of treatment in models of non-small cell lung cancer (NSCLC) via attenuation of p53 activity [41]. The similar actions of androgens and glucocorticoids on the function of p53 may be attributed to the knowledge that AR and glucocorticoid receptor (GR) are more evolutionarily related to each other than to the ER [1], suggesting an evolutionary pressure for this dichotomous regulation of p53 function. Although PR and AR are more evolutionarily related than GR and AR[42], suggesting that ER function may be dominant to PR function with respect to p53 regulation. Additionally, the studies of negative regulation by AR and GR were conducted in tissues not typically considered as hormone-responsive (e.g. liver and lung) [40, 41]. Furthermore, glucocorticoids are often used in concert with DNA damaging regimens to reduce side effects of chemotherapy [43]. Therefore, the negative impact of GR signaling on p53 activity may have broader implications on the strength and duration of a therapeutic response to chemotherapy in any tumor type, and not simply restricted to hormone-dependent malignancies. Taken together, these data indicate that ER and progesterone receptor (PR) signaling positively regulate p53, while AR and GR signaling negatively regulate p53 function. While it is unclear what the implications of these regulatory events are for tumor phenotypes and/or malignant progression, these functional interactions may be relevant when combining hormone therapy and DNA damaging therapeutic strategies in p53-positive tumors.

HORMONAL REGULATION OF DNA REPAIR

As outlined above, there are five basic categories of DNA damage repair [30–35]. To date, the majority of experimental evidence demonstrates that steroid hormones primarily regulate double-strand break (DSB) repair through non-homologous end joining (NHEJ) and homologous recombination (HR).

Non-homologous end joining (NHEJ)

NHEJ is the predominant pathway utilized to repair DSBs, which consists of a step-wise process of anchoring the broken ends of DNA to each other via the Ku70/Ku80/DNAPK protein complex, followed by end processing (if necessary), then ligation by the XRCC4/DNA ligase IV complex. To date, three independent studies have described the role of steroid hormones and their receptors in NHEJ, all of which implicate a positive regulation of NHEJ by NRs[44–46]. Both estrogens in BrCa and androgens in PCa were found to induce components of NHEJ. Each study emphasized a different component of NHEJ as being specifically responsible for steroid-induced DNA repair. In PCa model systems, DNAPK-cs (*PRKDC*) expression was found to be a directly regulated by AR, as androgen

stimulation elicited up-regulation of both mRNA and protein levels of PRKDC [45]. Additionally, androgens promoted DNAPK activity, directly implicating androgen signaling in positive regulation of DNA repair via NHEJ. A companion study implicated androgen/AR signaling in multiple DNA repair pathways, including NHEJ, via positive regulation of *XRCC4* and *XRCC5* [46]. Moreover, tumors from PCa patients undergoing neo-adjuvant androgen deprivation therapy (removal of male hormones) harbored decreased Ku70 levels and increased levels of DNA damage as determined by γ H2AX foci (an indication of DNA double strand breaks) after prostatectomy [44]. In BrCa model systems, it has been shown that estrogen signaling controls NHEJ via stimulation of NBS1 (Nibrin) expression through the concerted functions of c-Myc, p53, and the co-activators CBP (CREB binding protein) and SRC1 (Nuclear receptor coactivator 1) at the NBS1 gene locus [47]. Combined, these studies indicate that abrogation of NHEJ, either directly or through removal of positive regulation by steroid hormone signaling, sensitized cells to genotoxic stress, indicating the biological importance of this crosstalk. In summary, androgens and estrogens positively regulate NHEJ, and therapeutic inhibition of NRs in PCa and BrCa results in irreparable DSBs.

Homologous recombination (HR)

HR is the second most prevalent means of DSB repair that involves sensing, strand resection, DNA synthesis, which involves either strand invasion or displacement, and break resolution. Unlike the apparent positive regulation of NHEJ by steroid hormone signaling, experimental evidence suggests that steroid hormones have the capacity to both positively and negatively regulate HR. Several studies implicate androgen/AR and estrogen/ER in positive regulation of HR. In PCa, the AR-regulated prostatic tumor suppressor gene Nkx3.1 serves directly in DDR via activation of ATM and recruitment of the DNA repair machinery to sites of damage [48]. In melanoma, the tumor suppressor gene MEN1 and ER α bind to the promoters of RAD51 and BRCA1, therein activating transcription [49]. Conversely, ER β functions to place RAD51 into an inactive complex with insulin receptor substrate 1 (IRS1), thus diminishing HR function in medulloblastoma [50]. Additionally, ER β antagonism results in cisplatin resistance as a result of enhanced RAD51-associated DNA repair [51]. Although the opposite effects of ER α and ER β demonstrate complexity, this is not without precedent as ER α has pro-proliferative capacity in BrCa, while ER β is growth inhibitive in many cancer types [52, 53]. As with NHEJ, the majority of the reported functions for hormone signaling facilitate HR, providing further evidence that targeting NRs in combination with induction of DSBs is a viable therapeutic strategy in multiple tumor types. While the in vitro studies described above nominate hormone signaling pathways as direct regulators of DNA repair pathways, there is evidence that a number of DDR factors serve as modulators of steroid receptor function, frequently in feed-forward loops in which NRs drive repair factors that then serve to support NR transcriptional function.

DNA REPAIR FACTORS AS MODULATORS OF STEROID RECEPTOR FUNCTION

As outlined above, a number of hormone signaling pathways converge to regulate DDR, which has likely consequence for response to both DNA damaging agents and hormone-

based therapies. As discussed below, an emerging body of literature demonstrates that components of DDR serve to regulate the function of multiple NRs and the hormone-dependent transcriptional programs that NRs govern.

Progesterone receptor (PR)

Poly(ADP-ribose)-polymerase-1 (PARP-1) is an abundant nuclear enzyme that was first described having roles in the repair of DNA damage and genomic maintenance [54, 55]. However, PARP-1 was shown to harbor critical, context-dependent transcriptional regulatory functions in cancer [56]. In BrCa cells, cyclin-dependent kinase 2 (CDK2) is activated by progestin treatment. Activated CDK2 then phosphorylates PARP-1, which subsequently induces PARP-1 enzymatic function. Activation of PARP-1 via CDK2 is required for the progestin-stimulated PR transcriptional program [57]. Despite this important finding, it is not yet clear what the biological outcome of PARP-1 regulation of PR might be. However the impact of PARP-1 on PR function should be considered in clinical trials utilizing PARP inhibitors in BrCa moving forward. A major NHEJ component, the DNAPK subunit Ku70, also interacts with PR in a complex that contains PARP-1, and through auto-phosphorylation of DNAPK and subsequent phosphorylation of PR help to mediate PR transcriptional function[58], further implicating DDR proteins in general, and specifically PARP-1 in PR activity.

Estrogen receptor (ER)

PARP-1 has also been reported to bind to and poly(ADP-ribose)ylate (PARylate) ER. PARylation of ER is required for ER binding to target sequences, as well as for ER target gene expression [59]. However, as with PR, the biological impact of PARP-1 regulation of ER is still unclear.

Mediator of DNA damage checkpoint 1 (MDC1), another key player in DDR, has also been shown to regulate ER. MDC1 interacts with γ H2AX, serving to recruit the MRN complex (MRE22/RAD50/NBS1), which is critical in both NHEJ and HR [60]. Studies have implicated MDC1 in regulating ER, wherein MDC1 directly binds to and increases the transactivation potential of ER, and also resides at sites of ER activity on chromatin. Interestingly, MDC1 levels decrease as a function of BrCa progression, and knockdown of MDC1 results in increased tumorigenic phenotypes, suggesting that the MDC1-dependent ER transcriptional program actually blocks cancer progression [61, 62]. Based on the studies outlined above, part of the functional output of the DDR machinery is to positively regulate ER function (table 1).

Androgen receptor (AR)

As with ER, MDC1 interacts with AR at sites of AR transcriptional activity, supporting AR transcriptional function. Also, the MDC1-dependent AR transcriptome serves an anti-tumorigenic role, as MDC1 levels decrease with PCa progression, and knockdown of MDC1 results in increased cancer-associated phenotypes [62]. Given the roles of both ER and AR in tumor initiation and progression in BrCa and PCa, respectively, it will be of relevance to further dissect the mechanisms by which MDC1 seemingly renders the function of these NRs anti-tumorigenic.

In addition to MDC1, enzymes associated with post-translational modifications (specifically kinases) have been shown to regulate AR. ACK1 is an intracellular tyrosine kinase involved in signal transduction whose function is increased in several tumor types via multiple mechanisms. ACK1 has previously been demonstrated to phosphorylate AR, resulting in resistance to radiation via up-regulation of the DNA damage signaling protein ATM. In PCa patient specimens, it was found that ATM levels correlate with ACK1 activation status, and ATM levels increase with disease progression [63, 64]. These data suggest that ACK1 may be a potential target to increase the efficacy of radiation therapy in AR positive tumors, due to the potential of this kinase to regulate both AR and ATM.

PIAS1 (protein inhibitor of activated STAT (signal transducer and activator of transcription)-1) is a SUMO-E3 ligase whose function is requisite for DNA repair, in part through regulation of p53. PIAS1 is elevated in primary and metastatic PCa, as well as in cells resistant to DNA damage induced by taxanes, which target microtubules. It was reported that PIAS1 interacts with AR, resulting in AR stabilization, as well as increasing AR transcriptional activity and AR-driven cancer phenotypes [65]. As such, PIAS1 is an AR co-activating molecule with therapeutic potential in combination with DNA damage (table 1).

As described above, AR directly regulates the expression and activity of DNAPKcs, resulting in proper NHEJ and subsequent resistance to DNA damage induced by radiation. DNAPKcs is an important kinase critical for the resolution of DSBs via the NHEJ pathway, which was actually first described as being associated with a transcriptional regulatory complex containing Sp1 [66]. The AR-DNAPKcs pathway is a positive feedback loop, as evidence has shown that DNAPK interacts with AR and resides on chromatin at regulatory elements of AR target gene loci serving as an AR coregulator [45, 67, 68]. Furthermore, loss of DNAPK function, either through knockdown or pharmacological inhibition, results in selectively attenuated AR function. This “feed-forward” regulation of AR by DNAPK is likely of clinical significance, as it has been observed that DNAPK is the most highly deregulated kinase in advanced PCa, and is tightly associated with poor disease outcome [69]. The roles of DNAPK in DNA damage resolution as well as AR transcriptional function nominates the kinase as a therapeutic target, which is currently being explored in the clinical setting. Interestingly, the DNAPK complex component Ku70 also complexes with ER α , supporting ER α transcriptional function[70], and ER α transcriptionally activates DNAPKcs[71]. These data indicate that DNAPK might be a viable target in both ER-and AR-driven malignancies in combination with hormonal therapy.

In addition to these enzymes, two proteins associated with relief of torsional stress within chromatin have been implicated in AR transcriptional activation. DNA topoisomerase II β (TOP2 β) was reported to induce transient DSBs at multiple gene promoters (including NR target genes), which were required for hormone-regulated transcription[67]. These DSBs resulted in recruitment of a large number of DDR factors (both HR and NHEJ components) that assisted in the final transcriptional output. Subsequent studies have demonstrated that these transient DSBs generated by TOP2 β at genomic loci of AR transcriptional activity, have the capacity to bring about genetic rearrangements that are commonly found in PCa [21, 23, 24]. These rearrangements place an androgen responsive gene promoter proximal to

the transcriptional start site of oncogenic ETS family transcription factors, thus rendering ETS factors under the control of androgen signaling. These ETS fusions have also been shown to generate DNA damage in PCa models, which resulted in sensitivity to certain targeted therapeutics [68]. Additionally, evidence suggests that DNA topoisomerase I (TOP1) also supports AR transcriptional function at enhancers, rather than promoters. Rather than a DSB, TOP1 causes single-strand nicks, resulting in activation of androgen-responsive enhancers, and subsequent transcriptional activation of AR target genes [72]. Similar to TOP2 β , subsequent recruitment of other DDR factors was found to be requisite for full transcriptional activation. While these data implicate both TOP1 and TOP2 β in regulation of NR function, it remains unclear whether there is cross talk between the DDR components responsible for enhancer activation and the DDR components responsible for generating and repairing DSBs at promoters of actively transcribed genes.

Finally, it has been shown that PARP-1 is recruited to sites of AR function, and that PARP-1 enzymatic activity is necessary for complete AR transactivation of target genes [73]. Additionally, it was determined that pharmacological inhibition of PARP-1 activity results in diminished PCa progression in model systems [REF]. Combined, these data indicate that PARP-1 plays critical roles in positively regulating NR function in cancer, and may represent a node of therapeutic targeting in hormone-dependent cancer. This concept is currently being tested clinically in metastatic castration-resistant prostate cancer (CRPC) in multiple trials, one as a single agent for men that have progressed on multiple lines of therapy (TO-PARP) [74] the other in combination with next-generation hormone ablation (Abiraterone) (NCT01576172).

HORMONE-DNA REPAIR CROSSTALK IN CANCER: CLINICAL RELEVANCE

Combination therapy

Over the course of BrCa management, hormone therapy (such as tamoxifen and/or aromatase inhibitors) is used in combination with DNA damaging protocols [75]. DNA damaging chemotherapeutic drugs or radiation are used sequentially or simultaneously with hormone therapy in NR-positive disease [76]. Use of combination therapy largely depends on the molecular pathology of the tumors and established co-morbidities, as well as other factors [77].

In PCa, hormone therapy is used in combination with radiation and/or surgery for multiple steps in tumor progression: high risk localized disease, locally advanced, and metastatic disease [78, 79]. This strategy has been the standard of care for locally advanced disease, and until recently, the mechanism by which this combination is effective remained elusive. However, evidence suggests that AR activity is involved in radiation resistance, and by targeting AR through androgen ablation tumor cells are rendered sensitive to the DNA damage induced by radiation [45, 46]. Therapeutic use of hormone therapy prior to radiation in PCa patients has corroborated the supposition that AR regulates NHEJ via control of components of the DNAPK enzyme complex [80]. Additionally, the Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer (CHAARTED) trial has demonstrated that use of first line hormone therapy in combination with microtubule stabilizing agents (taxanes) for newly diagnosed metastatic PCa yields survival benefit to

patients (13.6 months), and will thus likely supplant the current standard of care [81]. Given the significant amount of data implicating a positive feed-forward loop between the DDR and hormone signaling networks, it is imperative that these important biological mechanisms be considered when either analyzing clinical trial results or in future development of combinatorial strategies to combat cancer.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In summary, a litany of evidence supports the contention that NRs positively regulate DNA repair, and that components of the DDR machinery serve dual roles on chromatin: as regulators of damage repair as well as modulators of transcription factor (especially NR) function. This complex bidirectional regulation is an emerging and exciting field of study that is critical to pursue, as hormone-dependent cancers are frequently treated with DNA damaging regimens, and new clinical data is emerging using agents that target certain DDR components that possess NR-regulatory capabilities.

While the observations outlined herein are provocative, a number of key questions remain. First, do the mechanisms that govern hormone signaling-DNA repair crosstalk elicit biological outcomes relevant to cancer management? Most studies have been mechanistic and laboratory-based, in nature. As such, defining the impact of this crosstalk on cancer-associated phenotypes in translational and clinical studies remains of the highest priority. Second, will exploitation of the NR-DDR networks yield therapeutic benefit? While several clinical studies indicate that there may be opportunities for targeting either NR function to sensitize to damage (as the case with hormone therapy and radiation in PCa), or targeting DNA repair directly in hormone-dependent cancer, as with PARP inhibitors (PARPi) in CRPC, it has yet to be determined whether targeting steroid-DDR crosstalk can be put into clinical practice for malignancies in general, including those not thought to be traditionally hormone-dependent. Third, are hormones/NRs functioning in innate or acquired resistance to standard chemotherapeutics used in cancer management? Data described herein indicates that hormones function to positively regulate DNA repair. As such, hormone pathways may be driving chemotherapy sensitivity via the capacity to protect from genotoxicity. Fourth, are DDR factors candidate biomarkers that predict response to therapy or tumor progression? The recent approval of PARPi for use in *BRCA*-mutant ovarian cancer [82], and the success of the TO-PARP trial [74] indicate a number of genomic aberrations of the DDR machinery have the capacity to inform treatment. However, not all tumors harboring DDR mutation are impacted by treatment, while some tumors without DDR aberrations also respond to treatment, thus indicating a need for further study. Functional analyses of DDR factors may also be informative in this regard. Fifth, can the DNA repair and transcriptional-regulatory functions of DDR factors be segregated mechanistically, biologically, or therapeutically? While pharmacological inhibition of DDR factors has the capacity to elicit DNA damage alone or in combination with chemotherapy, determining whether the DNA repair and transcriptional roles of DDR proteins are governed by distinct processes has the potential to elucidate whether targeting one or the other in isolation can be therapeutically beneficial. Sixth, what are the mechanistic underpinnings of the selective nature of the means by which the DDR and NRs functionally interact? Data described herein indicate that there is not a uniform, consistent paradigm that can be assigned to the means by which DDR

and NRs engage in cross-regulation. Further insight into how these mechanisms occur might strengthen implementation of both hormone therapy and chemotherapy. Finally, what is the contribution of DDR to transcriptional regulation outside of hormone nuclear receptors, and should this be considered when designing and interpreting clinical trials? While the focus of this review was to outline the mechanisms by which DDR influences NR function, it is becoming more apparent that the DDR machinery impacts a myriad of transcriptional events, many of which have yet to be fully defined mechanistically, biologically, or clinically. Overall, it is clear that there is significant bi-directional cross-communication between hormone signaling and DNA repair. Subsequent studies should endeavor to obtain increased mechanistic understanding of these events, determine whether they are universal and biologically important, and leverage this combined knowledge to benefit the management of human malignancies.

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Glossary

DNA damage response and repair (DDR)	refers to a network of cellular pathways involving surveillance proteins that monitor the integrity of DNA and function to repair DNA lesions by activating cell cycle checkpoints and DNA repair pathways. DDR helps prevent the generation of potentially deleterious mutations
DNA Strand Breaks	Single strand DNA breaks (SSBs) involve only one strand of the DNA double helix and are repaired via base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). Double strand DNA breaks (DSBs) involve both strands of the DNA helix and are typically repaired by homologous recombination (HR) or nonhomologous end-joining (NHEJ)
Homologous recombination (HR)	HR is the second most prevalent means of DSB repair that involves sensing, strand resection, DNA synthesis, which involves either strand invasion or displacement, and break resolution
Nonhomologous end-joining (NHEJ)	NHEJ is the predominant pathway utilized to repair DSBs, which consists of a step-wise process of anchoring the broken ends of DNA to each other via the Ku70/Ku80/DNAPK protein complex, followed by end processing (if necessary), then ligation by the XRCC4/DNA ligase IV complex

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Trends box

- There exists controversy whether hormones are genotoxic or are protective of damage.
- Hormone/nuclear receptor signaling positively regulates DNA double-strand break repair in cancer.
- Several components of the DNA damage response and repair machinery influence nuclear receptor transcriptional function in models of malignancy.
- DNA repair-hormone signaling crosstalk represents an under-appreciated and potentially vast opportunity for further studies in cancer biology: basic, translational, and clinical.

Figure 1. Nuclear Receptors (NRs) regulate key DNA repair factors, and DNA repair factors influence NR function. Top (above the hashed line): DNA repair factors shaded in blue are those which are positively regulated by the indicated NR as depicted by the arrow and + sign, or negatively regulated by the indicated NR as depicted by the block line. Bottom (below the hashed line): Indicated DNA repair factors known to harbor effects on NRs are indicated. Text depicts how these DNA repair factors regulate NR function, and the biological outcomes are indicated in italics. Abbreviations: ERα, estrogen receptor α; ERβ, estrogen receptor β; AR, androgen receptor; PR, progesterone receptor; PCa, prostate cancer; BrCa, breast cancer.

Table 1

DNA Repair-associated enzymes regulated NRs

Repair factor	Function on NR	Biological consequence	REF
TOP2 β (Topoisomerase 2 β)	Activates AR, ER, PR	None currently known	[67]
ACK1 (Tyrosine Kinase Non- Receptor Protein 2)	Activates AR	Increases w/ disease progression in PCa	[63, 64]
MDC1 (Mediator of DNA- Damage Checkpoint 1)	Activates AR and ER	Decreases w/ disease progression in PCa & BrCa	[60]
PIAS1 (Protein Inhibitor of Activated STAT-1)	Activates AR	Increased in metastases	[65]