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Review

Linking DNA Damage and Hormone Signaling Pathways in Cancer

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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 that the existence of crosstalk mechanisms linking the DDR machinery and hormone signaling pathways cooperate to influence both cancer progression and therapeutic response. These underlying mechanisms and their implications for cancer management will be discussed.

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.

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 NR antagonists. Conflicting data exist 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; see Glossary) 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.

DNA damage response and repair (DDR) pathways are complex, highly regulated biological processes that protect the genome from both low-level DNA damage induced by DNA

Trends

Controversy exists 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 underappreciated and potentially vast opportunity for further studies in cancer biology: basic, translational, and clinical.

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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 to repair **single-strand breaks** (SSBs) through base excision repair (BER), DSBs via either **homologous recombination (HR)** or **non-homologous 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 crosstalk 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: (i) directly via activation of the estrogen receptor ∝ (ER∝) and increased *TP53* mRNA expression [37]; (ii) by estrogens serving a rheostat function to modulate both p53 levels and activity [38]; or (iii) 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 summary, 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 (GR) 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 GR are more evolutionarily related to each other than to ER [1], suggesting an evolutionary pressure for this dichotomous regulation of p53 function. Although progesterone receptor (PR) and AR are more evolutionarily related than GR and AR [42], suggesting that ER function may be dominant to PR function with regard 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 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

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 non-homologous end-joining (NHEJ).

Homologous recombination (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.

Non-homologous end-joining (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.