Serican Journal of Medicine
2026, VOL. 3, NO. 1, 24976
https://doi.org/10.17161/sjm.v3i1.24976

Metabolic Reprogramming and DNA Damage Response in Prostate Cancer: Implications for Treatment

Kendall Simpson[1], Zhiguo Li[2], and Xiaoqi Liu[2*]

[1]Department of Biological Sciences, Eastern Kentucky University, Richmond, KY 40475, USA; [2]Department of Toxicology and Cancer Biology, University of Kentucky, Lexington, KY 40536, USA
*To whom correspondence should be addressed: Department of Toxicology and Cancer Biology, University of Kentucky, 1095 V.A. Drive, Lexington, KY 40536. Tel: 859-562-2006; Fax: 859-323-1059; Email: xiaoqi.liu@uky.edu.

ABSTRACT

Dysregulation of metabolism and the DNA damage response are two hallmarks of cancer. With respect to the former, although most cancer types exhibit increased glycolysis (the Warburg effect), this is not the case for prostate cancer. Accordingly, we review the unique metabolic features of prostate cancer, including androgen receptor signaling, glucose metabolism, treatment vulnerabilities, metformin, and combination therapies. With respect to the latter, we review genomic instability in cancer, DNA repair subtypes, the role of MRE11 in DNA double-strand break repair, and the potential regulation of MRE11 by PLK1-mediated phosphorylation.

ARTICLE HISTORY
Received: Jan. 6, 2026
Revised: Feb. 19, 2026
Accepted: Feb. 20, 2026

KEYWORDS
prostate cancer, Metformin, DNA damage response, Mre11

1. Prostate Cancer Metabolism

1.1. Introduction

Prostate Cancer (PCa) remains the most commonly diagnosed cancer among men in the United States (US) [1]. Diagnoses of PCa are predicted to escalate, illustrating the necessity for the novel development of therapeutic strategies [2]. After surgical and radiation intervention, androgen deprivation therapy (ADT) is the next line of treatment for PCa patients, unfortunately reoccurrence, often with metastatic properties, remains an issue [3]. This led to the development of Enzalutamide (Enz), a clinically used second-generation androgen receptor (AR) inhibitor that directly binds to AR and prevents cell proliferation [4]. Even with advanced strategies to combat this disease, patients gain resistance to this line of treatment and are left with minimal therapeutic options. This has led researchers to explore and repurpose various FDA-approved medications in hopes that discovery of a viable therapeutic outcome for Enz-resistant castration-resistant prostate cancer (CRPC). Although metabolic reprogramming and genomic instability are often discussed separately, they are closely interconnected with prostate cancer. Metabolic alterations influence redox balance and nucleotide availability, thereby affecting DNA damage repair, while persistent DNA damage signaling can further reshape metabolic pathways. Because androgen receptor (AR) signaling regulates both processes, understanding their crosstalk may uncover new therapeutic vulnerabilities in castration-resistant prostate cancer. To summarize these interactions, a schematic diagram (Figure 1) visualizes the molecular mechanisms of cancer metabolism and DNA damage repair in prostate cancer, highlighting their crosstalk and potential therapeutic targets. Metabolism and DNA repair are connected: energy and building blocks from metabolism are needed for DNA repair, and DNA damage can change metabolism. In prostate cancer, AR signaling affects both, which is why we discuss them together.

In recent studies, it has been seen that there is a metabolic switch in drug-resistant PCa, indicating a shift from glycolysis to oxidative phosphorylation [5]. To capitalize on this vulnerability, utilization of therapeutics that inhibit oxidative phosphorylation may be a novel avenue in treatment strategies [6]. Metformin, a commonly used FDA-approved therapy for the treatment of type 2 diabetes, which will be discussed later in detail, has recently come to light as a possible treatment strategy for many types cancers, in particular, PCa [7].

1.2 Disease etiology

As recent reports indicate, PCa leads as the highest estimated new cancer cases in men in the United States and is the second leading cause of cancer deaths [1]. Prostate cancer is typically characterized

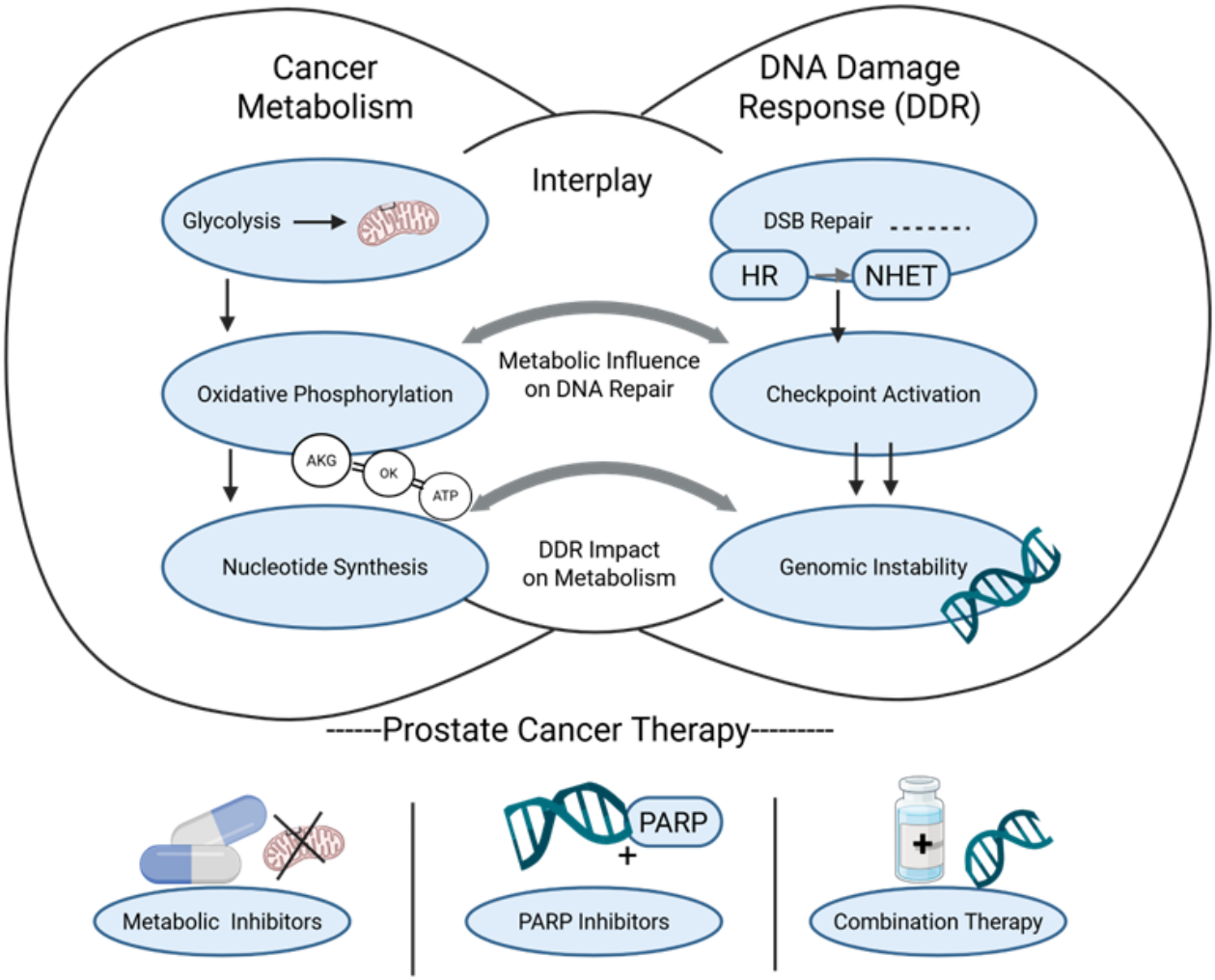

Figure 1. Crosstalk between metabolism and DNA repair in prostate cancer.
Metabolic pathways provide energy and building blocks for DNA repair, while DNA damage can influence metabolism. Therapies such as PARP inhibitors target these interconnected pathways to treat castration-resistant prostate cancer (CRPC).

by late age diagnosis and slow disease progression [8]. Age is the number one risk factor in the development of prostate cancer, while race and a genetic predisposition also play a large role in disease incidence [9]. The AR signaling pathway plays a critical role in PCa disease initiation and progression and is considered the main driver of PCa; however, there are various other mechanisms in which PCa progresses. Germline mutations in critical genes such as *ATM*, *BRCA2*, and *HOXB13* leave patients with a higher predisposition for the development of advanced PCa, in particular, metastatic PCa [10]. In addition, patients with single-nucleotide polymorphisms (SNPs) variants in cancer-related pathways also play a role in the initiation of this disease [11]. Following these genetic mutations and variations, the progression of PCa typically goes unnoticed for some time, as men with early stages of PCa are asymptomatic and are often overlooked [12]. Symptoms related to the urinary tract can often be easily dismissed or, in some cases, not related to a malignancy in the prostate and rather a benign hyperplasia (BPH), which causes trouble urinating and general discomfort [13]. As PCa continues to progress, men in later stages of this disease may experience symptoms including bone pain in the hips, back, and pelvis, as well as varying degrees of incontinence, which can lead to even further disease complications [12]. One of the critical tests for the initial diagnosis of PCa is a blood serum test for the detection of prostate-specific antigen (PSA) levels in the blood circulation [14]. PSA, typically only observed in the prostate gland, can enter circulation

following the breakdown of the basal membrane of the prostate gland during disease progression [15]. In general, biomarkers for cancer subtypes are rare and sometimes unreliable; however, this PSA biomarker is critical for determining disease progression. Following initial treatments for PCa, a second rise in serum PSA is a critical observation for determining cancer recurrence and a need for changing therapeutic strategies [16].

1.3 PCa treatment and castration-resistant prostate cancer (CRPC)

Depending on cancer stage, genetic factors, and recurrence, PCa treatments will vary vastly between patients or progression [17]. In the case of localized PCa, radical prostatectomy, or surgical removal of the prostate gland, coupled with radiation therapy, is the standard of care [18]. This treatment will typically decrease serum PSA and temporarily halt disease progression. Despite these treatments, a rise in serum PSA can indicate disease progression. Unfortunately, this leads clinicians to modify their treatment plans. AR activation is a key driver of prostate cancer initiation and progression. To block this signaling, clinicians often recommend chemical or surgical castration to deplete androgen levels. While this approach is initially effective, AR can eventually reactivate through alternative signaling pathways, leading to continued tumor growth. This leads the disease into a category labeled CRPC [19]. CRPC patients are typically treated with ADT to either inhibit AR signaling directly or to prevent androgen synthesis, resulting in a prevention of disease progression [20]. Despite the initial success of ADT, PCa has the capability to develop alternative mechanisms of tumorigenesis independent of AR signaling, categorizing it as mCRPC [21]. Within mCRPC, a recent report has categorized 4 different types of CRPC: AR-dependent, neuroendocrine (NE), Wnt-dependent, and stem cell-like CRPC [22]. Based on the results from this study, AR-dependent CRPC is characterized by high expression of AR and chromatin accessibility of AR-target genes such as *KLK2* [23]. NE CRPC samples have a high expression of the SYP gene, which codes for proteins critical in adrenal function, as well as a phenotype similar to small-cell carcinoma [24]. Both Wnt-dependent and stem cell-like CRPC have low expression of AR and NE genes and are harder to treat despite recent understanding [25-27]. Regardless of the subtype of CRPC, these genetic phenotypes of disease aid clinicians in the continued treatment of PCa. As the disease becomes more severe, treatment options become more limited, and often, patients with CRPC are treated with second-generation AR inhibitors (sgARi) such as apalutamide, darolutamide, and enzalutamide [28]. Of these, enzalutamide is currently the only therapy approved for metastatic CRPC; however, these therapies only extend patient survival, and drug resistance still occurs [29]. It is critical to determine novel treatment strategies for this niche of advanced drug-resistant mCRPC to increase overall patient survival and quality of life.

1.4 AR Signaling in PCa

Although there are numerous mechanisms in which cancer can be initiated, such as carcinogen exposure, mutation accumulation, and other factors, PCa initiation is typically characterized by gene alterations within the AR signaling axis [30]. Alterations in AR signaling play a pivotal role in the development and progression of PCa; however, AR signaling in homeostasis is critical for the development and maintenance of the prostate gland [31]. Canonically, testosterone and dihydrotestosterone (DHT) are the most predominant androgens in the development and maintenance of reproductive tissues [32]. Coincidentally, both testosterone and DHT can bind to AR in the cytoplasm as ligands activating AR signaling [31]. In the absence of an AR ligand, AR is bound to chaperone heat shock proteins (HSP) -90, -70, -56, and other chaperone proteins modulating the transcriptional activity of AR [33]. Following ligand binding, AR will undergo a conformational change, initiating AR homodimerization and ultimately, AR nuclear translocation [34]. AR, upon entering the nucleus, will recognize specific androgen response elements (ARE) in the promoter/enhancer regions of targeted genes. AR in this context functions as a transcription factor for genes such as PSA or probasin, a prostate-specific gene that acts as a marker for prostate differentiation and elucidates androgen action [35]. In the case of PCa, the transcriptional activity of AR on AREs can also initiate the transcription of other cancer-related genes contributing to disease progression [36].

There are several mechanisms by which aberrant AR signaling can induce PCa initiation and progression, the most common being splice variants of AR [37]. It has been reported that during the maturation of mRNA, splice variants of AR lacking a ligand-binding domain (LBD) often occur, rendering the variant constitutively active, leading to poor

survival rates [38]. AR-V7, one of the most abundant variants of AR, is truncated at the end of exon 3 and lacks the LBD and therefore can remain active in a ligand-independent manner [39]. AR-V7 still possesses the DNA-binding domain and nuclear localization signal of AR, thereby retaining the transcriptional factor functions of AR, which produces difficulties in treatment. PCa that possess these splice variants are intrinsically resistant to direct AR inhibitors such as enzalutamide [40]. In addition, the inordinate expression of AR can also be attributed to the biosynthesis of androgens, of which treatments such as abiraterone aim to inhibit. Despite various treatment options and strategies, PCa can develop methods in which to overcome these challenges, and drug resistance remains an issue of concern.

1.5 PCa glucose metabolism and treatment vulnerability

It is well known that many cancers exhibit what is considered the "Warburg Effect," which describes the altered means in which cancer cells undergo glucose metabolism [41]. Cancer cells tend to rely on aerobic glycolysis and, therefore, lactate production as the main method of utilizing glucose. Lactate fermentation is a less efficient method in which adenosine 5'-triphosphate (ATP) can be produced from a single molecule of glucose and bypasses the need for the mitochondrial production of ATP [42]. This is the opposite method in which normal cells utilize glucose, where aerobic respiration occurs, and the cells rely on oxidative phosphorylation (OXPHOS) to produce the majority of the cell's energy needs [5]. The utilization of glycolysis, pyruvate oxidation, the Krebs cycle, and OXPHOS to produce the ATP needed to maintain cellular function is different in cancer cells, and the reasoning is still unknown [43]. In the case of advanced PCa, it has been recently documented that these cancer cells rely on oxidative phosphorylation (OXPHOS) rather than lactate production [5]. This contrast with the Warburg effect in most cancers is illustrated in Figure 2A, highlighting AR-driven regulation of mitochondrial function and potential therapeutic targets such as metformin. Unlike most cancers, advanced prostate cancer cells rely on oxidative phosphorylation instead of glycolysis. This is driven by AR signaling, which controls genes for mitochondrial function and energy production, linking metabolism directly to tumor growth and therapy response. PCa cells utilize a proton gradient in the inner mitochondrial membrane to drive chemiosmosis and thereby ATP production. Many complex proteins in the electron transport chain are critical for this process [44]. These differences in glucose metabolism introduce a possible vulnerability in the cancer cells that may be exploited in novel treatment strategies. One strategy to therapeutically exploit this metabolic dependence is the use of agents that disrupt oxidative phosphorylation, such as metformin.

1.6 Metformin

One possible mechanism by which we can inhibit OXPHOS is the administration of metformin. Metformin is a biguanide that was originally approved for the treatment of non-insulin-dependent diabetes mellitus, or type 2 diabetes, in 1994 [45]. For patients with type 2 diabetes, metformin is utilized to control glycemia by lowering blood glucose levels in the presence of insulin resistance [46]. Metformin's primary mechanism of lowering blood glucose levels comes from decreasing hepatic glucose output and thereby reducing gluconeogenesis [45]. Specifically, metformin activates the AMP-activated protein kinase (AMPK), which plays a critical role in maintaining energy homeostasis in the cell [47]. Ultimately, following activation of AMPK, the cell will switch from an anabolic state to a catabolic state, shutting down energy synthesis pathways and restoring energy balance [47]. In addition to metformin's effect on AMPK, metformin has also been observed to inhibit complex I in the electron transport chain of OXPHOS, preventing ATP production via chemiosmosis, effectively impacting aerobic respiration [48].

The concept of utilizing metformin as a cancer treatment gained traction after the observation that diabetic patients taking metformin had a decreased cancer incidence and cancer-related mortality [49]. In addition, as the most commonly prescribed therapy for type II diabetes patients, metformin has an excellent safety profile with limited side effects [50]. In recent years, the investigation of metformin treatment, particularly in PCa, has been explored as a possible treatment option for advanced CRPC [51]. As an inhibitor of OXPHOS, metformin may be useful in treating advanced CRPC as a method for exploiting the abnormal mechanism of glucose metabolism for cancers. In addition, the metformin-mediated activation of the AMPK pathway has been shown to inhibit the activation of the mammalian target of rapamycin (mTOR) and protein synthesis pathways [52]. Considering the effect of metformin on glycemic control, how is it that we can speculate the use of

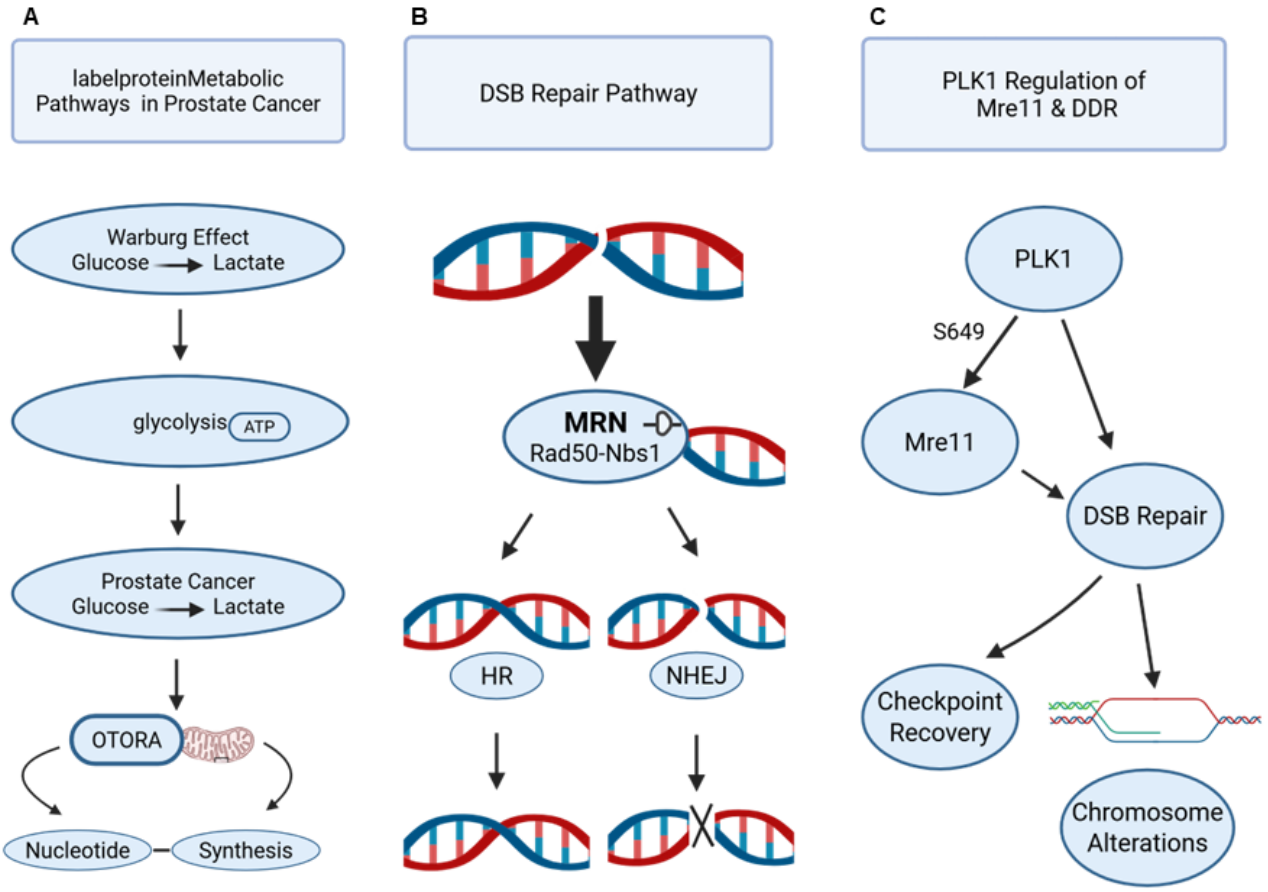

Figure 2. Prostate cancer metabolism and DNA double-strand break repair.
(A) Prostate cancer cells use glucose differently from typical cancer cells. Instead of relying on glycolysis (Warburg effect), they depend on oxidative phosphorylation (OTORA) to produce energy and building blocks for growth. (B) Double-strand breaks (DSBs) in DNA are recognized and processed by the MRN complex (Rad50-Nbs1), which directs repair through either homologous recombination (HR) or non-homologous end joining (NHEJ). HR results in accurate repair using a homologous template, whereas NHEJ directly ligates DNA ends, which may lead to small insertions or deletions. (C) PLK1 phosphorylates Mre11 to modulate DSB repair. This regulation affects checkpoint recovery and can lead to chromosomal alterations if repair is incomplete or defective. Arrows indicate the direction of regulation or influence between components.

metformin as a cancer treatment despite the absence of non-insulin-dependent diabetes mellitus? Recent reports indicate that metformin's anti-tumorigenic effects are independent of its effects in glycemic control; however, metformin is considered safe for use in the literature despite hypoglycemic events that can occur from taking this drug [53].

1.6 Conclusion of using combination therapies in PCa

The logistics in the development of novel therapeutic drugs come with a monumental financial cost and investment of time; therefore, developing treatment strategies that utilize FDA-approved drugs with promising safety profiles is an attractive target for cancer therapeutics [54]. Utilization of FDA-approved therapies continues to be a topic of interest in the development of novel treatment strategies, as these drugs have already been approved and tested for safety and toxicity in humans [55]. In the case of PCa, enzalutamide exhibited high efficacy both in clinical trials and in practice, despite the observation of resistance in advanced CRPC. Historically, combination treatment approaches have assisted in overcoming certain resistant obstacles and provided late-stage patients with additional options. Ideally, combination treatments possess the ability to attack various targets in order to control or slow the growth of the malignancy [56]. In this study, we aimed to combine metformin with enzalutamide treatment as a means of increasing the efficacy of enzalutamide as well as repurposing an FDA-approved drug to halt the energy production in cancer cells. In addition to AR-targeted combinations, pairing metabolic mod-

ulators like metformin with DNA repair–targeting agents, such as PARP inhibitors, may further sensitize prostate cancer cells. By simultaneously disrupting energy production and DNA damage repair, this approach could exploit tumor vulnerabilities and help overcome therapy resistance in advanced PCa.

2 DNA damage repair in cancer

2.1 Genomic instability in cancer

Historically, the importance of maintaining genomic stability has been investigated for decades and is a foundational concept in the maintenance of homeostasis. Evolutionarily, proteins critical for DNA repair and maintenance are largely conserved across species from yeast to humans, which highlights the importance of regulation of this intricate cellular process [57]. As a hallmark of cancer, genomic instability can occur in different mechanisms, such as TP53 inactivation pathways and mutations in caretaker genes such as tumor suppressors and oncogenes [58]. The critical role of the DDR is to prevent mutations by repairing damaged DNA; however, some mutations are hereditary. Certain germline mutations, such as BRCA mutations in breast cancer, are passed from parental genetics, and therefore, the breast cells of these patients are more vulnerable to developing cancer [59]. In this example, BRCA genes are tumor suppressors, so when mutated, DNA repair is inhibited, and irregularities occur in DNA synthesis [60]. Similarly, many other cancers depend on the alteration of the DNA damage response to induce a cancerous phenotype [61].

In contrast, many therapeutics on the market aim to induce DNA damage in the cancer to induce apoptosis and cell death [62]. Cisplatin, a commonly used platinum drug for the treatment of various cancers, is demonstrated to induce nephrotoxicity in treated cells by forming cisplatin adducts [63]. By forming interstrand crosslinks in the DNA, the treated cells either need to attempt to repair the DNA or, if the damage is too great, simply progress to apoptosis [64]. By this mechanism, cisplatin affects cancer cells; however, as normal cells also have DNA, there are unwanted side effects [64]. Many other agents have a mechanism of action like cisplatin in that they disrupt the genomic stability and induce cell death, highlighting the importance of genome maintenance.

2.2 DNA repair subtypes

Historically, there are 5 main subtypes of DNA damage repair, 2 of which repair double-strand breaks and the other 3 typically repair single-strand breaks [65]. There are many nuances between nucleotide excision repair, base excision repair, and mismatch repair, of which all of them recognize different DNA damage lesions; however, all 3 of these pathways typically repair single-strand breaks [66]. Homologous recombination (HR) and non-homologous end joining (NHEJ) are the 2 primary mechanisms in which cells repair DSB damage [67]. In the case of DSB, both the parental and daughter strands of DNA are severed, leaving either a clean break where homologies are close in proximity to each other or a larger DSB where sections of the DNA are either missing or removed. HR relies on utilizing the overhanging strands of both strands of DNA to identify the homologies and repair the damage in a relatively error-free manner [68]. In the case where DNA damage is so large and homologies/sections of DNA are lost, NHEJ will simply repair the DNA by trimming and ligating the ends together; however, this will most likely result in mutations, gene loss, chromosomal rearrangements, or other genomic alterations [69].

2.3 MRE11A in DSB repair

MRE11A, a critical protein in the MRN complex, is crucial for both HR and NHEJ pathways of DSB repair. At both stalled replication forks and sites of DSB damage, meiotic recombination 11 homolog 1 a (MRE11A) protein forms a complex with Rad50 and Nbs1 called the MRN complex, orchestrating some of the first responses in the DDR [70]. NBS1 is first recruited to the site of DNA damage through the interaction with the cell cycle checkpoint protein Rad17 [71]. Once at the site of damage, MRN will recruit and activate ATM and ATR for further downstream DDR signaling [72]. Finally, activated ATM phosphorylates the mediator of DNA damage checkpoint 1 (MDC1) protein for continued amplification of the signal and recruitment of additional MRN complexes [73]. The intricacies of NHEJ and HR repair differ in proteins involved, both upstream and downstream; however, the MRN complex and signaling activation of ATM/ATR are present in both types of repair.

In NHEJ, DSBs are mended by DNA end-joining with minimal processing. Within this process, Ku heterodimer, consisting of both Ku70 and Ku80, will bind at the DNA ends and recruit DNA-PKCs, which are critical for phosphorylating various proteins responsible for DNA end processing and ligation [74]. The initial DNA end resection requires both the endonuclease and exonuclease activity of

the MRN complex, as well as other enzymes, such as CtIP, PARP1, FEN1, and DNA ligases I and III, for the completion of repair or regulation of the process via WRN or BLM helicase [75-77].

In HR, DSBs are extensively resected, specifically creating 3' ssDNA overhangs, which in turn prevent NHEJ [78]. MRE11A, within the MRN complex, will initiate and license DNA resection through endonuclease activity by creating a nick for the exonuclease activity to resect the DNA in a 3' to 5' direction [79]. At the nick, 5' to 3' nucleases such as EXO1 and helicases such as BLM or WRN will promote extended resection away from the nick and create a 3' overhang of DNA [80]. This process creates the homologies needed for homologous recombination and ultimate DNA repair [77]. A schematic overview of DSB repair pathways, highlighting the central role of Mre11a, is shown in Figure 2B.

2.4 Cellular function and regulation of PLK1

Polo-like kinase 1 (PLK1), an essential protein in the regulation of the cell cycle, has been demonstrated as highly upregulated in cancers [81-83]. Canonically, PLK1 is a key mitotic regulator where it functions in regulating mitotic entry, centrosome maturation, spindle assembly, APC/C regulation, and cytokinesis [84]. Typically, transcriptional levels of PLK1 are tightly regulated in G1 phase by tumor protein P53, cyclin-dependent kinase inhibitor 1, and retinoblastoma protein [85]. It has been reported that p53 and p21 regulate the expression of PLK1 via direct binding with PLK1, preventing its transcription [86]. As evidence has grown demonstrating that PLK1 may play a role in various cancer progression and initiation, non-canonical functions of PLK1 have been explored.

2.5 Regulation of MRE11A via phosphorylation by PLK1

Generally, the phosphorylation of Mre11a is essential for progressing many critical functions of DSB repair, as well as affecting cell cycle and chromosomal rearrangement [87]. Mre11a can be phosphorylated by Cdk1 during mitosis, suggesting the necessity of Mre11a activation during the cell cycle [88]. Following these implications, our lab sought to understand if PLK1 also played a role in the regulation of MRE11A. Through *in vitro* kinase assays, our lab was able to demonstrate that PLK1 phosphorylates MRE11A at S649 during G2 phase DNA damage recovery [89]. The network of PLK1-mediated regulation of Mre11a and its impact on DDR is summarized in Figure 2C. In addition, PLK1-meditated phosphorylation enhances the subsequent phosphorylation of MRE11A at S689 by CK2, and these two phosphorylation events drive premature checkpoint termination and reduced DNA repair [89].

2.6 Thymic lymphoma as a model to observe changes in DDR

As DNA DSB can be an effective means to induce mutagenesis, various DNA damage inducers are utilized in cancer therapies, particularly ionizing radiation damage. In the treatment of carcinogenesis, scientists and clinicians have utilized ionizing radiation (IR) to induce DNA damage as a means of inducing apoptosis in cancer cells [90]. IR treatments can be an effective means to treat carcinogenesis; however, patients often experience severe side effects, including secondary cancer formation [91]. The current gold standard model in studying the mechanisms of radiation-induced carcinogenesis utilizes a fractionated low-dose radiation exposure treatment [92]. In addition to understanding carcinogenesis mechanisms, it is also understood that split low-dose irradiation is a reliable method for the induction of thymic lymphoma [93]. One of the benefits of utilizing the split low-dose irradiation model in investigating DNA repair responses to DNA damage is the ease with which disease progression can be monitored. In thymic lymphoma, T cells developed in the thymus are normally in an immature state, expressing CD8a and CD4 simultaneously [94]. Following release from the thymus, mature T cells express either CD8a, CD4, or neither in a normal system. In the case of thymic lymphoma, immature T cells, expressing CD8a and CD4 together, are found in circulation as an indicator of disease progression [95]. These T cell changes are normally in response to an accumulation of DNA damage within the hematopoietic system, which is indicative of an increased mutational burden and a lack of DNA repair. Although thymic lymphoma arises in a different tissue context, this model provides mechanistic insight into how defective DDR signaling and DSB repair drive tumorigenesis. Because similar DDR alterations, including ATM dysfunction and impaired DSB repair, are observed in advanced prostate cancer, findings from this model offer translational insight into how disruptions in proteins such as MRE11A and PLK1 may contribute to genomic instability and therapy resistance in PCa.

Disclosure of Potential Conflicts of Interest: The authors declare no potential conflicts of interest.

Reference

1. Siegel RL, Miller KD, Wagle NS, Jemal A: **Cancer statistics, 2023**. *CA Cancer J Clin* 2023, **73**(1):17–48. doi:10.3322/caac.21763:
2. Rawla P: **Epidemiology of Prostate Cancer**. *World J Oncol* 2019, **10**(2):63–89. doi:10.14740/wjon1191: PMC6497009.
3. Sharifi N, Gulley JL, Dahut WL: **Androgen deprivation therapy for prostate cancer**. *JAMA* 2005, **294**(2):238–244. doi:10.1001/jama.294.2.238:
4. Bambury RM, Scher HI: **Enzalutamide: Development from bench to bedside**. *Urol Oncol* 2015, **33**(6):280–288. doi:10.1016/j.urolonc.2014.12.017:
5. Cutruzzola F, Giardina G, Marani M, Macone A, Paiardini A, Rinaldo S, Paone A: **Glucose Metabolism in the Progression of Prostate Cancer**. *Front Physiol* 2017, **8**:97. doi:10.3389/fphys.2017.00097: PMC5318430.
6. Chen CL, Lin CY, Kung HJ: **Targeting Mitochondrial OXPHOS and Their Regulatory Signals in Prostate Cancers**. *Int J Mol Sci* 2021, **22**(24). doi:10.3390/ijms222413435: PMC8708687.
7. Mayer MJ, Klotz LH, Venkateswaran V: **Metformin and prostate cancer stem cells: a novel therapeutic target**. *Prostate Cancer Prostatic Dis* 2015, **18**(4):303–309. doi:10.1038/pcan.2015.35:
8. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ: **Age and cancer risk: a potentially modifiable relationship**. *Am J Prev Med* 2014, **46**(3 Suppl 1):S7–15. doi:10.1016/j.amepre.2013.10.029: PMC4544764.
9. Bechis SK, Carroll PR, Cooperberg MR: **Impact of age at diagnosis on prostate cancer treatment and survival**. *J Clin Oncol* 2011, **29**(2):235–241. doi:10.1200/JCO.2010.30.2075: PMC3058279.
10. Brandao A, Paulo P, Teixeira MR: **Hereditary Predisposition to Prostate Cancer: From Genetics to Clinical Implications**. *Int J Mol Sci* 2020, **21**(14). doi:10.3390/ijms21145036: PMC7404100.
11. Knudsen BS, Vasioukhin V: **Mechanisms of prostate cancer initiation and progression**. *Adv Cancer Res* 2010, **109**:1–50. doi:10.1016/B978-0-12-380890-5.00001-6:
12. Dunn MW, Kazer MW: **Prostate cancer overview**. *Semin Oncol Nurs* 2011, **27**(4):241–250. doi:10.1016/j.soncn.2011.07.002:
13. Ziada A, Rosenblum M, Crawford ED: **Benign prostatic hyperplasia: an overview**. *Urology* 1999, **53**(3 Suppl 3a):1–6. doi:10.1016/s0090-4295(98)00532-9:
14. Sturge J, Caley MP, Waxman J: **Bone metastasis in prostate cancer: emerging therapeutic strategies**. *Nat Rev Clin Oncol* 2011, **8**(6):357–368. doi:10.1038/nrclinonc.2011.67:
15. Berish RB, Ali AN, Telmer PG, Ronald JA, Leong HS: **Translational models of prostate cancer bone metastasis**. *Nat Rev Urol* 2018, **15**(7):403–421. doi:10.1038/s41585-018-0020-2:
16. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC: **Natural history of progression after PSA elevation following radical prostatectomy**. *JAMA* 1999, **281**(17):1591–1597. doi:10.1001/jama.281.17.1591:
17. Gomella LG, Johannes J, Trabulsi EJ: **Current prostate cancer treatments: effect on quality of life**. *Urology* 2009, **73**(5 Suppl):S28–35. doi:10.1016/j.urology.2009.03.003:
18. Shoag JE, Nyame YA, Gulati R, Etzioni R, Hu JC: **Reconsidering the Trade-offs of Prostate Cancer Screening**. *N Engl J Med* 2020, **382**(25):2465–2468. doi:10.1056/NEJMsb2000250: PMC7491201.
19. Chandrasekar T, Yang JC, Gao AC, Evans CP: **Mechanisms of resistance in castration-resistant prostate cancer (CRPC)**. *Transl Androl Urol* 2015, **4**(3):365–380. doi:10.3978/j.issn.2223-4683.2015.05.02: PMC4708226.
20. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, Henry AM, Joniau S, Lam TB, Mason MD *et al*: **EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer**. *Eur Urol* 2017, **71**(4):630–642. doi:10.1016/j.eururo.2016.08.002:
21. He L, Fang H, Chen C, Wu Y, Wang Y, Ge H, Wang L, Wan Y, He H: **Metastatic castration-resistant prostate cancer: Academic insights and perspectives through bibliometric analysis**. *Medicine (Baltimore)* 2020, **99**(15):e19760. doi:10.1097/MD.0000000000019760: PMC7220391.
22. Tang F, Xu D, Wang S, Wong CK, Martinez-Fundichely A, Lee CJ, Cohen S, Park J, Hill CE, Eng K *et al*: **Chromatin profiles classify castration-resistant prostate cancers, suggesting therapeutic targets**. *Science* 2022, **376**(6596):eabe1505. doi:10.1126/science.abe1505: PMC9299269.

23. Hannu K, Johanna M, Ulf-Hakan S: **KLK-targeted Therapies for Prostate Cancer**. *EJIFCC* 2014, **25**(2):207–218. PMC4975297.
24. Beltran H, Rickman DS, Park K, Chae SS, Sboner A, MacDonald TY, Wang Y, Sheikh KL, Terry S, Tagawa ST *et al*: **Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets**. *Cancer Discov* 2011, **1**(6):487–495. doi:10.1158/2159-8290.CD-11-0130: PMC3290518.
25. Yamada Y, Beltran H: **Clinical and Biological Features of Neuroendocrine Prostate Cancer**. *Curr Oncol Rep* 2021, **23**(2):15. doi:10.1007/s11912-020-01003-9: PMC7990389.
26. Ojo D, Lin X, Wong N, Gu Y, Tang D: **Prostate Cancer Stem-like Cells Contribute to the Development of Castration-Resistant Prostate Cancer**. *Cancers (Basel)* 2015, **7**(4):2290–2308. doi:10.3390/cancers7040890: PMC4695890.
27. Yokoyama NN, Shao S, Hoang BH, Mercola D, Zi X: **Wnt signaling in castration-resistant prostate cancer: implications for therapy**. *Am J Clin Exp Urol* 2014, **2**(1):27–44. PMC4219296.
28. Hoffman-Censits J, Kelly WK: **Enzalutamide: a novel antiandrogen for patients with castrate-resistant prostate cancer**. *Clin Cancer Res* 2013, **19**(6):1335–1339. doi:10.1158/1078-0432.CCR-12-2910:
29. Wang Y, Chen J, Wu Z, Ding W, Gao S, Gao Y, Xu C: **Mechanisms of enzalutamide resistance in castration-resistant prostate cancer and therapeutic strategies to overcome it**. *Br J Pharmacol* 2021, **178**(2):239–261. doi:10.1111/bph.15300:
30. Litwin MS, Tan HJ: **The Diagnosis and Treatment of Prostate Cancer: A Review**. *JAMA* 2017, **317**(24):2532–2542. doi:10.1001/jama.2017.7248:
31. Lonergan PE, Tindall DJ: **Androgen receptor signaling in prostate cancer development and progression**. *J Carcinog* 2011, **10**:20. doi:10.4103/1477-3163.83937: PMC3162670.
32. Handelsman DJ: **Androgen Physiology, Pharmacology, Use and Misuse**. In: *Endotext*. edn. Edited by Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, *et al*. South Dartmouth (MA); 2000.
33. Smith DF, Toft DO: **Minireview: the intersection of steroid receptors with molecular chaperones: observations and questions**. *Mol Endocrinol* 2008, **22**(10):2229–2240. doi:10.1210/me.2008-0089: PMC2582531.
34. van Royen ME, Cunha SM, Brink MC, Mattern KA, Nigg AL, Dubbink HJ, Verschure PJ, Trapman J, Houtsmuller AB: **Compartmentalization of androgen receptor protein-protein interactions in living cells**. *J Cell Biol* 2007, **177**(1):63–72. doi:10.1083/jcb.200609178: PMC2064112.
35. Bennett NC, Gardiner RA, Hooper JD, Johnson DW, Gobe GC: **Molecular cell biology of androgen receptor signalling**. *Int J Biochem Cell Biol* 2010, **42**(6):813–827. doi:10.1016/j.biocel.2009.11.013:
36. Jin HJ, Kim J, Yu J: **Androgen receptor genomic regulation**. *Transl Androl Urol* 2013, **2**(3):157–177. doi:10.3978/j.issn.2223-4683.2013.09.01: PMC4165347.
37. Lu C, Luo J: **Decoding the androgen receptor splice variants**. *Transl Androl Urol* 2013, **2**(3):178–186. doi:10.3978/j.issn.2223-4683.2013.09.08: PMC4209743.
38. Hornberg E, Ylitalo EB, Crnalic S, Antti H, Stattin P, Widmark A, Bergh A, Wikstrom P: **Expression of androgen receptor splice variants in prostate cancer bone metastases is associated with castration-resistance and short survival**. *PLoS One* 2011, **6**(4):e19059. doi:10.1371/journal.pone.0019059: PMC3084247.
39. Hu R, Dunn TA, Wei S, Isharwal S, Veltri RW, Humphreys E, Han M, Partin AW, Vessella RL, Isaacs WB *et al*: **Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer**. *Cancer Res* 2009, **69**(1):16–22. doi:10.1158/0008-5472.CAN-08-2764: PMC2614301.
40. Sobhani N, Neeli PK, D'Angelo A, Pittacolo M, Sirico M, Galli IC, Roviello G, Nesi G: **AR-V7 in Metastatic Prostate Cancer: A Strategy beyond Redemption**. *Int J Mol Sci* 2021, **22**(11). doi:10.3390/ijms22115515: PMC8197232.
41. Liberti MV, Locasale JW: **The Warburg Effect: How Does it Benefit Cancer Cells?** *Trends Biochem Sci* 2016, **41**(3):211–218. doi:10.1016/j.tibs.2015.12.001: PMC4783224.
42. Doherty JR, Cleveland JL: **Targeting lactate metabolism for cancer therapeutics**. *J Clin Invest* 2013, **123**(9):3685–3692. doi:10.1172/JCI69741: PMC3754272.
43. Kozal K, Jozwiak P, Krzeslak A: **Contemporary Perspectives on the Warburg Effect Inhibition in Cancer Therapy**. *Cancer Control* 2021, **28**:10732748211041243. doi:10.1177/10732748211041243: PMC8474311.

44. Fontaine E: **Metformin-Induced Mitochondrial Complex I Inhibition: Facts, Uncertainties, and Consequences**. *Front Endocrinol (Lausanne)* 2018, **9**:753. doi:10.3389/fendo.2018.00753: PMC6304344.
45. Bailey CJ, Turner RC: **Metformin**. *N Engl J Med* 1996, **334**(9):574–579. doi:10.1056/NEJM199602293340906:
46. Foretz M, Guigas B, Viollet B: **Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus**. *Nat Rev Endocrinol* 2019, **15**(10):569–589. doi:10.1038/s41574-019-0242-2:
47. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F: **Cellular and molecular mechanisms of metformin: an overview**. *Clin Sci (Lond)* 2012, **122**(6):253–270. doi:10.1042/CS20110386: PMC3398862.
48. LaMoia TE, Shulman GI: **Cellular and Molecular Mechanisms of Metformin Action**. *Endocr Rev* 2021, **42**(1):77–96. doi:10.1210/endrev/bnaa023: PMC7846086.
49. Noto H, Goto A, Tsujimoto T, Noda M: **Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis**. *PLoS One* 2012, **7**(3):e33411. doi:10.1371/journal.pone.0033411: PMC3308971.
50. Masarwa R, Brunetti VC, Aloe S, Henderson M, Platt RW, Filion KB: **Efficacy and Safety of Metformin for Obesity: A Systematic Review**. *Pediatrics* 2021, **147**(3). doi:10.1542/peds.2020-1610:
51. Whitburn J, Edwards CM, Sooriakumaran P: **Metformin and Prostate Cancer: a New Role for an Old Drug**. *Curr Urol Rep* 2017, **18**(6):46. doi:10.1007/s11934-017-0693-8: PMC5405102.
52. Dowling RJ, Zakikhani M, Fantus IG, Pollak M, Sonenberg N: **Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells**. *Cancer Res* 2007, **67**(22):10804–10812. doi:10.1158/0008-5472.CAN-07-2310:
53. Rizos CV, Elisaf MS: **Metformin and cancer**. *Eur J Pharmacol* 2013, **705**(1-3):96–108. doi:10.1016/j.ejphar.2013.02.038:
54. Sleire L, Forde HE, Netland IA, Leiss L, Skeie BS, Enger PO: **Drug repurposing in cancer**. *Pharmacol Res* 2017, **124**:74–91. doi:10.1016/j.phrs.2017.07.013:
55. Zhang Z, Zhou L, Xie N, Nice EC, Zhang T, Cui Y, Huang C: **Overcoming cancer therapeutic bottleneck by drug repurposing**. *Signal Transduct Target Ther* 2020, **5**(1):113. doi:10.1038/s41392-020-00213-8: PMC7331117.
56. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H: **Combination therapy in combating cancer**. *Oncotarget* 2017, **8**(23):38022–38043. doi:10.18632/oncotarget.16723: PMC5514969.
57. Aravind L, Walker DR, Koonin EV: **Conserved domains in DNA repair proteins and evolution of repair systems**. *Nucleic Acids Res* 1999, **27**(5):1223–1242. doi:10.1093/nar/27.5.1223: PMC148307.
58. Aguilera A, Garcia-Muse T: **Causes of genome instability**. *Annu Rev Genet* 2013, **47**:1–32. doi:10.1146/annurev-genet-111212-133232:
59. Casey G: **The BRCA1 and BRCA2 breast cancer genes**. *Curr Opin Oncol* 1997, **9**(1):88–93. doi:10.1097/00001622-199701000-00014:
60. Patel KJ, Yu VP, Lee H, Corcoran A, Thistlethwaite FC, Evans MJ, Colledge WH, Friedman LS, Ponder BA, Venkitaraman AR: **Involvement of Brca2 in DNA repair**. *Mol Cell* 1998, **1**(3):347–357. doi:10.1016/s1097-2765(00)80035-0:
61. Sieber OM, Heinimann K, Tomlinson IP: **Genomic instability--the engine of tumorigenesis?** *Nat Rev Cancer* 2003, **3**(9):701–708. doi:10.1038/nrc1170:
62. Salmaninejad A, Ilkhani K, Marzban H, Navashenaq JG, Rahimirad S, Radnia F, Yousefi M, Bahmanpour Z, Azhdari S, Sahebkar A: **Genomic Instability in Cancer: Molecular Mechanisms and Therapeutic Potentials**. *Curr Pharm Des* 2021, **27**(28):3161–3169. doi:10.2174/1381612827666210426100206:
63. Dasari S, Tchounwou PB: **Cisplatin in cancer therapy: molecular mechanisms of action**. *Eur J Pharmacol* 2014, **740**:364–378. doi:10.1016/j.ejphar.2014.07.025: PMC4146684.
64. Ranasinghe R, Mathai ML, Zulli A: **Cisplatin for cancer therapy and overcoming chemoresistance**. *Heliyon* 2022, **8**(9):e10608. doi:10.1016/j.heliyon.2022.e10608: PMC9489975.
65. Friedberg EC: **DNA damage and repair**. *Nature* 2003, **421**(6921):436–440. doi:10.1038/nature01408:
66. Abbotts R, Wilson DM, 3rd: **Coordination of DNA single-strand break repair**. *Free Radic Biol Med* 2017, **107**:228–244. doi:10.1016/j.freeradbiomed.2016.11.039: PMC5443707.
67. Kanaar R, Hoeijmakers JH, van Gent DC: **Molecular mechanisms of DNA double-strand break**

repair. *Trends Cell Biol* 1998, **8**(12):483–489. doi:10.1016/s0962-8924(98)01383-x:

68. San Filippo J, Sung P, Klein H: **Mechanism of eukaryotic homologous recombination**. *Annu Rev Biochem* 2008, **77**:229–257. doi:10.1146/annurev.biochem.77.061306.125255:
69. Burma S, Chen BP, Chen DJ: **Role of non-homologous end joining (NHEJ) in maintaining genomic integrity**. *DNA Repair (Amst)* 2006, **5**(9-10):1042–1048. doi:10.1016/j.dnarep.2006.05.026:
70. Lamarche BJ, Orazio NI, Weitzman MD: **The MRN complex in double-strand break repair and telomere maintenance**. *FEBS Lett* 2010, **584**(17):3682–3695. doi:10.1016/j.febslet.2010.07.029: PMC2946096.
71. Wang Q, Goldstein M, Alexander P, Wakeman TP, Sun T, Feng J, Lou Z, Kastan MB, Wang XF: **Rad17 recruits the MRE11-RAD50-NBS1 complex to regulate the cellular response to DNA double-strand breaks**. *EMBO J* 2014, **33**(8):862–877. doi:10.1002/embj.201386064: PMC4194111.
72. McCarthy-Leo C, Darwiche F, Tainsky MA: **DNA Repair Mechanisms, Protein Interactions and Therapeutic Targeting of the MRN Complex**. *Cancers (Basel)* 2022, **14**(21). doi:10.3390/cancers14215278: PMC9656488.
73. Wu L, Luo K, Lou Z, Chen J: **MDC1 regulates intra-S-phase checkpoint by targeting NBS1 to DNA double-strand breaks**. *Proc Natl Acad Sci U S A* 2008, **105**(32):11200–11205. doi:10.1073/pnas.0802885105: PMC2516250.
74. Mahaney BL, Meek K, Lees-Miller SP: **Repair of ionizing radiation-induced DNA double-strand breaks by non-homologous end-joining**. *Biochem J* 2009, **417**(3):639–650. doi:10.1042/BJ20080413: PMC2975036.
75. Shamanna RA, Lu H, de Freitas JK, Tian J, Croteau DL, Bohr VA: **WRN regulates pathway choice between classical and alternative non-homologous end joining**. *Nat Commun* 2016, **7**:13785. doi:10.1038/ncomms13785: PMC5150655.
76. Grabarz A, Guirouilh-Barbat J, Barascu A, Pennarun G, Genet D, Rass E, Germann SM, Bertrand P, Hickson ID, Lopez BS: **A role for BLM in double-strand break repair pathway choice: prevention of CtIP/Mre11-mediated alternative nonhomologous end-joining**. *Cell Rep* 2013, **5**(1):21–28. doi:10.1016/j.celrep.2013.08.034:
77. Syed A, Tainer JA: **The MRE11-RAD50-NBS1 Complex Conducts the Orchestration of Damage Signaling and Outcomes to Stress in DNA Replication and Repair**. *Annu Rev Biochem* 2018, **87**:263–294. doi:10.1146/annurev-biochem-062917-012415: PMC6076887.
78. Krejci L, Altmannova V, Spirek M, Zhao X: **Homologous recombination and its regulation**. *Nucleic Acids Res* 2012, **40**(13):5795–5818. doi:10.1093/nar/gks270: PMC3401455.
79. Lafrance-Vanasse J, Williams GJ, Tainer JA: **Envisioning the dynamics and flexibility of Mre11-Rad50-Nbs1 complex to decipher its roles in DNA replication and repair**. *Prog Biophys Mol Biol* 2015, **117**(2-3):182–193. doi:10.1016/j.pbiomolbio.2014.12.004: PMC4417436.
80. Tomimatsu N, Mukherjee B, Deland K, Kurimasa A, Bolderson E, Khanna KK, Burma S: **Exo1 plays a major role in DNA end resection in humans and influences double-strand break repair and damage signaling decisions**. *DNA Repair (Amst)* 2012, **11**(4):441–448. doi:10.1016/j.dnarep.2012.01.006: PMC3319278.
81. Ramani P, Nash R, Sowa-Avugrah E, Rogers C: **High levels of polo-like kinase 1 and phosphorylated translationally controlled tumor protein indicate poor prognosis in neuroblastomas**. *J Neurooncol* 2015, **125**(1):103–111. doi:10.1007/s11060-015-1900-4:
82. Tut TG, Lim SH, Dissanayake IU, Descallar J, Chua W, Ng W, de Souza P, Shin JS, Lee CS: **Upregulated Polo-Like Kinase 1 Expression Correlates with Inferior Survival Outcomes in Rectal Cancer**. *PLoS One* 2015, **10**(6):e0129313. doi:10.1371/journal.pone.0129313: PMC4457812.
83. Zhang R, Shi H, Ren F, Liu H, Zhang M, Deng Y, Li X: **Misregulation of polo-like protein kinase 1, P53, and P21WAF1 in epithelial ovarian cancer suggests poor prognosis**. *Oncol Rep* 2015, **33**(3):1235–1242. doi:10.3892/or.2015.3723:
84. Barr FA, Sillje HH, Nigg EA: **Polo-like kinases and the orchestration of cell division**. *Nat Rev Mol Cell Biol* 2004, **5**(6):429–440. doi:10.1038/nrm1401:
85. McKenzie L, King S, Marcar L, Nicol S, Dias SS, Schumm K, Robertson P, Bourdon JC, Perkins N, Fuller-Pace F *et al*: **p53-dependent repression of polo-like kinase-1 (PLK1)**. *Cell Cycle* 2010, **9**(20):4200–4212. doi:10.4161/cc.9.20.13532: PMC3055203.
86. Zhu H, Chang BD, Uchiumi T, Roninson IB: **Identification of promoter elements responsible for transcriptional inhibition of polo-like**

kinase 1 and topoisomerase IIalpha genes by p21(WAF1/CIP1/SDI1). *Cell Cycle* 2002, **1**(1):59–66.
87. Lu R, Zhang H, Jiang YN, Wang ZQ, Sun L, Zhou ZW: **Post-Translational Modification of MRE11: Its Implication in DDR and Diseases**. *Genes (Basel)* 2021, **12**(8). doi:10.3390/genes12081158: PMC8392716.
88. Simoneau A, Robellet X, Ladouceur AM, D'Amours D: **Cdk1-dependent regulation of the Mre11 complex couples DNA repair pathways to cell cycle progression**. *Cell Cycle* 2014, **13**(7):1078–1090. doi:10.4161/cc.27946: PMC4013159.
89. Li Z, Li J, Kong Y, Yan S, Ahmad N, Liu X: **Plk1 Phosphorylation of Mre11 Antagonizes the DNA Damage Response**. *Cancer Res* 2017, **77**(12):3169–3180. doi:10.1158/0008-5472.CAN-16-2787: PMC5504882.
90. Ryan JL: **Ionizing radiation: the good, the bad, and the ugly**. *J Invest Dermatol* 2012, **132**(3 Pt 2):985–993. doi:10.1038/jid.2011.411: PMC3779131.
91. Mavragani IV, Nikitaki Z, Souli MP, Aziz A, Nowsheen S, Aziz K, Rogakou E, Georgakilas AG: **Complex DNA Damage: A Route to Radiation-Induced Genomic Instability and Carcinogenesis**. *Cancers (Basel)* 2017, **9**(7). doi:10.3390/cancers9070091: PMC5532627.
92. Boniver J, Humblet C, Rongy AM, Delvenne C, Delvenne P, Greimers R, Thiry A, Courtoy R, Defresne MP: **Cellular aspects of the pathogenesis of radiation-induced thymic lymphomas in C57 BL mice (review)**. *In Vivo* 1990, **4**(1):41–43.
93. Mothersill C, Seymour C: **Low-dose radiation effects: experimental hematology and the changing paradigm**. *Exp Hematol* 2003, **31**(6):437–445. doi:10.1016/s0301-472x(03)00078-x:
94. Owen DL, Sjaastad LE, Farrar MA: **Regulatory T Cell Development in the Thymus**. *J Immunol* 2019, **203**(8):2031–2041. doi:10.4049/jimmunol.1900662: PMC6910132.
95. Introcaso CE, Kim EJ, Gardner J, Junkins-Hopkins JM, Vittorio CC, Rook AH: **CD8+ epidermotropic cytotoxic T-cell lymphoma with peripheral blood and central nervous system involvement**. *Arch Dermatol* 2008, **144**(8):1027–1029. doi:10.1001/archderm.144.8.1027: