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Prostate Cancer and DNA Genes Repair: What Should an Oncologist Know? – A Narrative Review

Fernando Santos de Azevedo[1,2*], Lanúscia Morais de Santana Sá[3], Uirá Maíra de Resende[2], Augusto Ribeiro Gabriel[2], Elisângela de Paula Silveira Lacerda[1]

[1]Graduate Program in Genetics and Molecular Biology, Federal University of Goiás, Goiânia, Brazil

[2]Unidade Onco-hematológica, Hemolabor, Goiânia, Brazil

[3]Hospital das Clínicas, Universidade Federal de Goiás, Goiânia, Brazil

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***Corresponding author:**
Fernando Santos de Azevedo

E-mail address:
fernandoazevedooncologia@gmail.com

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A B S T R A C T

Prostate cancer is a very prevalent disease in men, especially in Western countries. The treatment of this neoplasm, both localized and locally advanced, is based on the clinical risk analysis (Gleason, tumor size, PSA, and other factors) and is founded on surgery and/or radiotherapy with or without androgen blockade with a GnRH analog (hormone gonadotropin releaser). However, in patients who invariably progress to a metastatic disease scenario, the tumors may present a heterogeneous behavior, depending on whether or not they are sensitive to androgen blockade therapy. Due to the poor prognosis of the metastatic castration-resistant scenario, current research carried out in the molecular biology and genetics field has identified several gene alterations associated with the development of prostate cancer, which correlate with clinical risk, therapeutic predictive responses, and prognosis. Among the associated gene alterations, the genes of the DNA repair pathway are correlated with diseases that present: a higher risk of recurrence; early metastasis; worse cancer-specific survival; familial risk, and predictive responses to new targeted therapies. Therefore, the breast cancer susceptibility genes, BRCA1 and BRCA2 (and other variants), present in the DNA repair machinery are being investigated to provide more (and better) therapeutic options for the treatment of the disease in the advanced scenario. This review was aimed to describe the malignant prostate disease, especially with regard to DNA repair mechanisms, genomic analysis of prostate cancer, predictive and prognostic implications, as well as on the development of poly-(ADP-ribose) polymerase (PARP) inhibitors, synthetic lethality mechanisms, and BRCAness phenomenon.

1. Introduction

Prostate cancer is the second most common neoplasm in men, being the sixth leading cause of mortality in the world and the second in Western countries.[1-3] Most patients with malignant prostatic neoplasia have a natural history that includes the disease: localized, locally advanced, metastatic castration-sensitive, and non-metastatic and metastatic castration-resistant.[2-6] Even with advances in genomic analysis, the prognosis of the setting resistant to metastatic castration remains bleak, and a better understanding of the molecular characterization of this pathology is necessary.[2-6] Recently, the literature has shown that understanding changes in DNA repair genes, both of somatic and germinal origin, can lead to new therapeutic advances.[6-10] In this narrative review, we will explore the landscape of malignant prostatic disease, covering topics related to DNA repair mechanisms, the genomic analysis of prostate cancer, the predictive and prognostic implications, as well as the development of

poly(ADP-ribose) polymerase inhibitors (PARP), synthetic lethality mechanisms and BRCAness concept. Therefore, this work is relevant because it can help oncologists to better understand the prognostic and predictive genetic alterations in response to prescribed treatments of prostate cancer. This review aimed to describe the malignant prostate disease, especially with regard to DNA repair mechanisms, genomic analysis of prostate cancer, predictive and prognostic implications.

Overview of malignant prostate neoplasm

Prostate cancer is the second most common neoplasm in men globally and the second commonest cause of death in Western countries.[1,2] It is known that African American family history and race are the main risk factors. Modern series estimate that men with first-degree relatives affected by this neoplasm are approximately 14.5% more likely to develop the disease than the general population, thus suggesting a prominent role for genetic factors.[1-4] More than 100 gene locus of susceptibility to prostate cancer have been identified, and many of them have variable penetrance and are used to classify the risk of disease from potentially lethal to indolent behavior.[5,6]

Sporadic prostate cancer comprises 85% of all cases of this neoplasm, while only 15% have an associated familial and/or hereditary component.[3-7] Sporadic cases can arise from somatic mutations accumulating in the prostate tissue, while the hereditary is initiated and propagated by mutations in germ cells. The definition of heredity in prostate cancer includes the cases: at least three generations, three first-degree relatives, or two affected first-degree relatives before age 55.[3,4,8]

The natural history of the disease comprises the setting localized, locally advanced, disease sensitive to androgen deprivation therapy, generally with a good prognosis and progression to the case of the extremely aggressive and lethal disease known as a castration-resistant disease, metastatic or non-metastatic.[2-10]

Advances in genomics have allowed the identification of genes (BRCA2, ATM, PALB2, among others) responsible for carcinogenesis, cancer progression, and disease subclassification, in addition to the usual histological descriptions. Recent studies have established that androgen signaling continues to play a major role in both tumor progression and resistance to targeted therapy.[8-10,12,13]

Malignant prostate disease is characterized by a high rate of genomic instability and chromosomal rearrangements. The most frequent is the overexpression of the androgen receptor (AR) promoter associated with genes from the transcription factor (ETS) family.[5-10,12,13] Other common genetic aberrations in primary tumors include loss of the tensin homologous phosphatase (PTEN) gene in 17%, alteration in the HOXB13 gene, ranging from 0.7 to 6%, nuclear protein point mutations (SPOP) in 11%, mutations in TP53 and MYC corresponding to 11 and 7%, respectively.[10,12-15]

Genomic progress (identification of the genes mentioned above) has been provided by next-generation sequencing (NGS) analyses to study intratumoral, intra-, and inter-patient molecular heterogeneity.[8-10,12,13,15] Data from several studies have shown that genetic abnormalities in DNA repair pathways (deoxyribonucleic acid) have been implicated in the pathogenesis, predictive responses, and prognosis of prostate cancer.[1-10,12,13,15]

The analyzed studies report that breast cancer susceptibility genes (BRCA 1 and 2) and other genes, such as RAD51C, ATM, ATR, BARD1, BRIP1, NBN, RAD51B, RAD51D, RAD54L, CHEK2, CDK12, MMR genes (MSH1, MLH1, MSH2, and MSH6), FANCD2 - and genetic damage to other repair pathways, both of somatic and germinal origin, are associated with increased risk and severity of the neoplasm, even in early stages of the disease.[1-10,12,13,15-37]

Recent advances in the genomic panorama evaluation of prostate cancer, as discussed above, have allowed the discovery of new therapeutic targets with modest gains in survival in a setting of advanced disease, resistance to androgen therapy, and failure to classical treatments, such as abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T,

Radium-223, Lutecio-PSMA, among other approaches.[6,28,38-51]

DNA damage repair mechanisms

Cell DNA damage can be caused by primary or secondary mechanisms, the latter being provoked by endogenous (reactive oxygen species, for example) and exogenous sources, such as ionizing radiation, chemicals, toxins, and ultraviolet radiation.[1-8] Damage response pathways are necessary to maintain DNA stability, activate the repair process, and induce apoptosis when necessary, preventing genomic instability with consequent disease proliferation, survival, and mutagenesis.[8-10]

Activation of damaged DNA repair pathways is orchestrated by several proteins, including P53, BRCA1, BRCA 2, PARP, NBS1, Ku70/80, MDC1, Chk1, and Chk2, which act in immediate response to genomic injury. Depending on the type and severity of the damage, responses vary between cell cycle arrest, senescence, or activation of different cell death programs, such as mitotic catastrophe, apoptosis, autophagy, and necrosis.[2-6] P53 is one of the crucial proteins for the initiation and progression of senescence or apoptosis secondary to genetic damage, and, once active, it regulates an enormous amount of proteins, namely: kinase-dependent cyclin inhibitors, p53AiP1, via BCL2 associated with X (BAX), miRNAs, caspases-2 and other JNK-associated signaling pathways promoting cell death.[8,9]

Cells of eukaryotic organisms have involved at least five major groups of repair pathways in maintaining genome integrity; these are: i) base excision repair (BER); ii) nucleotide excision repair (NER) and its sub-pathways (global genomic and transcription-coupled); iii) mismatch repair (MMR); iv) homologous repair (HR); v) non-homologous end joining (NHEJ),[2-10,12-19,21-32,34-37,39,44,49,52,53] as shown in Figure 1.

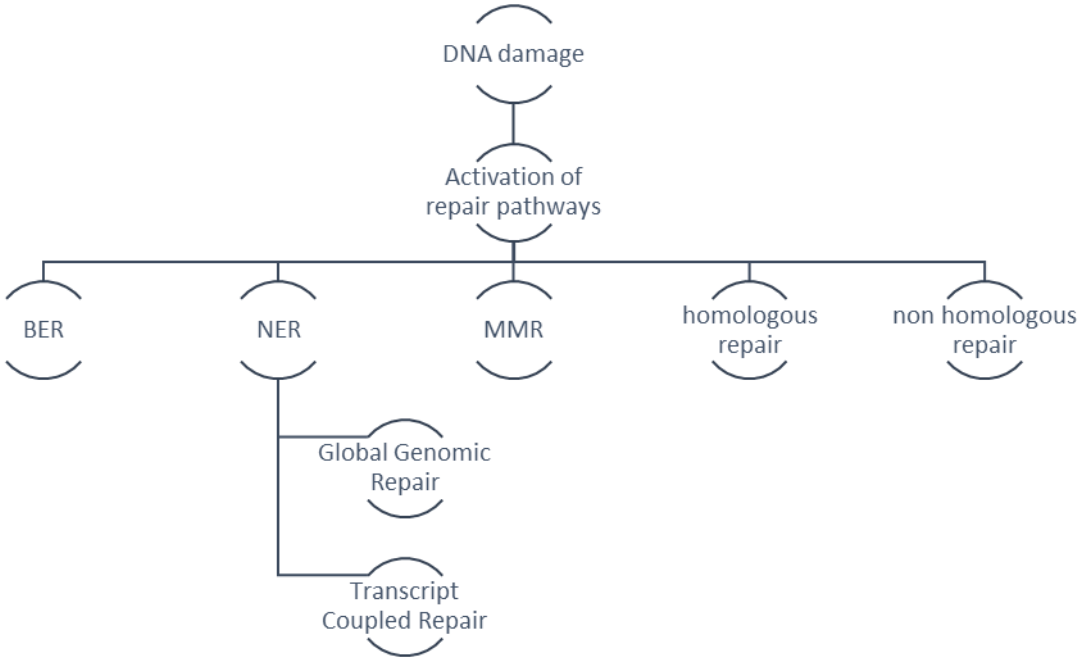

Figure 1. Schematic representation of the 5 major DNA repair groups.[2–8,35]

Excision by base repair

Excision by base repair is considered a critical pathway for the repair of small lesions in bases that distort the DNA double-strand due to oxidation, methylation, and deamination. This process is presented in Figure 2a. The excision by base repair is a pathway primarily active in the G1 phase of the cell cycle and is initiated by one of 11 DNA glycosylases that removes the damaged base and creates an abasic (apurinic/apyrimidinic) site. At this site, specific

endonucleases (APE 1/2, XRCC1, Pol-Beta) incise the DNA and insert single or multiple bases, followed by sealing by DNA ligase.[6,8-10,12,14,20,50]

In the base excision repair process, PARP proteins are fundamental. PARP proteins consist of a family of 17 multifunctional proteins, the most expressed and important of which are: PARP1 and 2. PARP1 binds to damaged single-stranded DNA, activating its catalytic function, with a consequent synthesis of negatively charged PAR chains, PARylation phenomenon, using NAD+ as a cofactor, which leads to the recruitment of DNA repair effectors, promoting chromatin remodeling and single-stranded repair. After the repair process is completed, allosteric changes occur in the DNA structure, and PARP proteins are released, returning to the inactive phases.[6,44,50,52,53]

Excision by nucleotide repair

Nucleotide repair excision promotes the repair of larger DNA lesions that can distort the double helix, for example, ultraviolet radiation, cisplatin, and benzopyrenes, as presented in Figure 2b. Depending on the type of injury, a repair can occur through two sub-pathways.[6-10] The first subpathway is called total genomic repair, in which the entire genome is tracked, including transcriptionally inactive areas, with recognition of damage and activation of the XP pathway (xeroderma pigmentosum), the complementation protein C, the repair protein sensitive to radiation 23B (RAD23B) and CETRIN2, promoting single strand repair. Once the damage is recognized, these proteins bind to the transcriptional unit of the initiation factor, promoting DNA opening and repair by DNA polymerase, followed by the closing of the lesion by DNA ligases.[6,7,9,48] The second subpathway, called transcription-coupled repair, is responsible for identifying the lesion and recruiting specific proteins called CSA (Cockayne Syndrome A) and CSB (Cockayne Syndrome B), which conscript other proteins forming a complex that translocates RNA polymerase, exposing the lesions and promoting repair.[2-10,12,44,51]

MMR (mismatch repair)

The mismatch repair process is represented in Figure 2c. Base mismatch, either by insertions or deletions, can occur during replication. In these cases, the repair occurs through the mismatch repair (base mismatch repair). The main genes encoding the pathway are MHS2, MSH5, MLH1, PMS1, PMS2, and MLH3.[6-10,12] During repair, proteins are grouped into heterodimers forming complexes that act as mediators so that other proteins can remove base mismatches, such as PCNA, RFC, and EXO1, which are responsible for removing incompatible sites and repairing them.[2-9]

Homologous recombination

Double-stranded damage is mainly repaired by the homologous pathway, which occurs in the S and G2 phases of the cell cycle, having as characteristics a slow, accurate, and error-free repair, justified by the use of a template strand during the process.[2-6] When DNA damage is identified, either by single-stranded or double-stranded non-repair, the MRN, KU, and PARP complexes are recruited, which will activate the ATM and ATM-RAD3 (ATR) proteins, which mediate the signaling for the proteins CHEK2 and BRCA1, promoting cell cycle arrest and initiation of repair through BRCA2 and RAD5 effectors.[1,3,6,41.51] The homologous recombination repair process is depicted in Figure 2d.

The BRCA1 and BRCA2 genes, discovered in 1990 and 1995, are located on chromosomes 17q21 and 13q12.3, respectively. These genes are known to promote tumor suppression and are involved in transcriptional regulation and double-stranded repair. BRCA1 is directly involved in the homologous recombination and stabilization process of TP53, while BRCA2 promotes the recruitment of the RAD51 recombinase (protein activated in the repair process).[1,3,6,38,48-52,54-56] Thus, after the formation of the MRN/KU/PARP complex, it will be reallocated by RAD51 in the BRCA-dependent pathway to complete the recombinase action and damage repair.[6,49]

Non-homologous end joining (NHEJ)

The NHEJ repair occurs specifically in the G1 phase. The NHEJ repair process is depicted in Figure 2d. Despite being a process faster than the homologous repair, it is prone to errors, as it does not use a DNA template strand and, thus, there is a consequent genomic instability.[6,38,47,54] The NHEJ pathway is activated by double-stranded lesions or accumulation of single-stranded errors, which are recognized and linked to Ku70/80 or PARP1 heterodimers, which promote the recruitment of catalytic proteins to form a single complex. Thus, this complex recruits more proteins, such as ARTEMIS and other protein kinases, to promote repair. DNA polymerases bind to the damaged region (repairing them) and later to ligases that seal the DNA strand.[1-7,28,38,44]

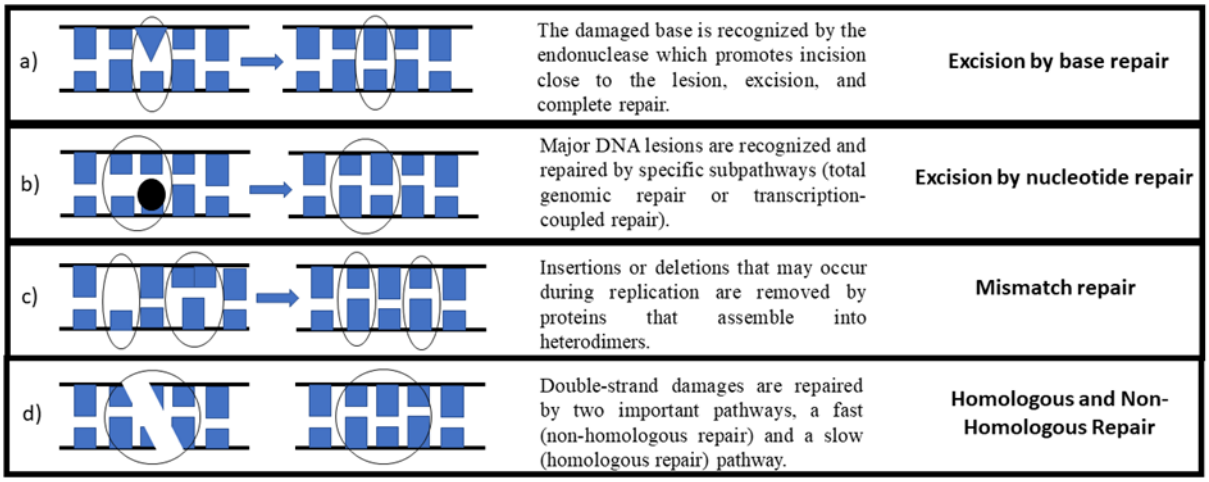

Figure 2. Detailed representation of the five major DNA repair groups.[2-8,35]

Genomic analysis of prostate cancer

Somatic and germline mutations in DNA genes repair

Prostate cancer has a high rate of genomic instability, including chromosomal amplifications, deletions, and rearrangements. Usually, the instability results from DNA damage, evidencing, once again, the role played by the repair genes in prostate carcinogenesis.[6,8–10,28,38,54] When considering mutations in these repair genes, it is important to determine their prevalence. Despite a significant number of studies, the results are inconsistent and do not answer the question entirely. However, it is known that the frequency is related to the stage of the disease (localized or metastatic), to the somatic and germ origin, and to other correlated factors.[1–3,10,18,20,24,29,30,32,34–37,44,45,54,57,58]

Germline mutations, particularly in the BRCA1 and BRCA2 genes, confer greater susceptibility to other neoplasms (breast, ovary, and pancreas, for example) and are associated with diseases of adverse prognosis. In prostate cancer, in a localized disease scenario, mutations in the BRCA1 and BRCA2 genes range from 0.0 – 2.0% and 0.6 – 4.7%, respectively. On the other hand, in the metastatic scenario, there is a greater representation of mutation in the BRCA2 gene, with a frequency of 5.35%.[1–5,10,13,15–17,19,21–26,54,59–62]

In addition to the aforementioned germline alterations, somatic mutations (TP53, TMPRSS2, ETS fusion, and others) that drive tumor carcinogenesis can also be found 42. In addition, there is a particular interest in DNA repair pathway genes (BRCA1 and BRCA2). A series of studies evaluating patients in the localized and metastatic setting showed frequencies of 3.0% and 1.0%, and 13.3% and 0.7% for BRCA 2 and BRCA 1, respectively.[1–10,12,16–38,44,54,57–60,62]

The studies analyzed show that evaluating only the metastatic scenario, without selecting for sensitivity or

resistance to hormone deprivation therapy, the prevalence of mutations in somatic [germ] repair genes ranges from 10.0 – 16.5% [11,4 – 11.8%].[1–10,44,54] Despite the variation in data on mutational prevalence in repair genes, regardless of the scenario analyzed (sensitive or resistant to metastatic castration) or the type of mutation (somatic or germline), it is important to encourage genetic testing in order to assess the prognosis, prediction of response to targeted therapy and genetic counseling both individual and family.[1–8,10,14,16,19–21,25–28,32–43,45,47–49,51–56,58–61,63]

Prognostic and predictive implications

It is known that the pathogenesis and natural history of prostate cancer with some genetic aberration in DNA repair genes have been associated with worse clinical outcomes. Available data show that both localized and metastatic diseases that carry mutations mainly in breast cancer susceptibility genes 1 and 2 and other variants of the homologous recombination process are more often associated with higher Gleason scores (greater than 8), more advanced clinical tumor staging (T3 or T4), nodal involvement, younger age to onset, metastasis at diagnosis and lower survival, compared to the ones that do not carry mutations. Some other characteristics analyzed in patients who had mutations in BRCA1, BRCA 2, and ATM involves cancer-specific mortality at a younger age. In localized prostate cancer, BRCA2 germline mutation had faster progression to a metastatic scenario and castration-resistant disease at a frequency >50%, thus being considered an independent risk factor of worse prognosis.[2,3,10,28,33,52–54,61]

Clinical development of PARP inhibitors in prostate cancer

As previously mentioned, PARPs are a set of nuclear enzymes that catalyze ribosylation in eukaryotic cells and are involved in the translational process of various proteins. Furthermore, PARPs promote single-stranded DNA damage and repair signaling. PARP1 catalyzes the breakdown of NAD+, taking it as a substrate to make a protein receptor along with histones and other chromatin-associated proteins to form the PAR chain, a phenomenon known as "PARylation". This complex phenomenon mediates DNA repair by modifying the chromatid structure and repairing DNA associated with other molecules.[1,8,9,54]

The rationale for the development of PARP inhibitors arose from the premise that, by blocking the enzyme, there would be a collapse of the base repair pathway, resulting in an accumulation of DNA damage, which would promote errors in the replication forces, with consequent damage to the double-strand, sensitizing tumor cells to additional DNA damage. PARP inhibitors promote entrapment in the catalytic domain, preventing the enzyme from being released from its repair site. In normal cells, due to the efficient damage correction mechanism, PARP inhibition is of no significant importance, however when associated with another genetic defect/deficiency, particularly mutation in BRCA genes or other genes of the damage repair pathway, promotes cell death, following the principle of synthetic lethality mechanism, which will be described in section.[4.78–10,28,42,44,51]

Among the new PARP enzyme inhibitor drugs developed are olaparib, niraparib, rucaparib, veliparib, and talazoparib. These drugs are in different stages of development in clinical studies and, in general analysis, shows that in prostate cancer in the castration-resistant scenario, the use of these drugs promoted an improvement in quality of life, an increase in progression-free survival and response rate, in addition to other clinical outcomes analyzed in specific studies.[1,3–10,12–19,21–37,39–47,49–52,54–58,62.]

BRCAness concept

Some tumors share phenotypes and genetic properties similar to the BRCA-mutated neoplasms, particularly aberrations/deficiencies in damage repair pathways. The phenotype can be induced by alterations in genes that modulate the repair by homologous recombination (ATM, ATR, CHEK1, RAD51, and FANC, among others) or pharmacologically, by blocking enzymes responsible for single-stranded repair.[6–10,14,15,28,38,44,48,52,54,56]

With the advancement of genetics and DNA analysis processes, a new genomics approach has been developed, consisting of the evaluation of gene signatures, whose rationale is the evaluation of DNA instability through the number of chromosomal breaks between adjacent regions, loss of heterozygosidase, and a number of telomeric imbalances. The results of the analyzes are graded, and if the tumor presents an index of gene instability favoring the deficiency in the repair processes, it may benefit from the use of specific target therapy. Despite being a promising approach, studies are still in progress to obtain analytical validation.[6,8–10,48]

Synthetic lethality

Synthetic lethality is a phenomenon in which one gene allele, when inactivated by mutation, does not present cytotoxicity, but when in combination, that is, with the simultaneous inactivation of two genes, either pharmacologically or intrinsically induced, it promotes cell death. This phenomenon has attracted researchers because it explains the sensitivity of tumor cells to certain drugs that act in specific processes of DNA repair.[1–3,5–10,13,14,16,17,19–30,32–43,45,47–56,58–61,63.]

As previously presented, the BRCA1 and BRCA2 genes contribute to double-stranded DNA repair. PARP enzymes are responsible for single-stranded damage correction and recruit different pathways for error correction. When PARP is pharmacologically blocked, single-stranded damage cannot be repaired, promoting double-stranded damage becoming lethal when the cell has some deficiency in the homologous repair pathway with consequent genomic instability, cycle arrest, and cell death.[1,2,6,10,14,15,33,48,49,52,53,61]

2. Conclusion

Prostate cancer is a molecularly heterogeneous disease where in addition to genetic aberrations in the androgen receptor pathway, ETS fusion, and changes in TMRPSS2 genes, changes in DNA repair pathways are also involved in the genomic instability mechanisms of this neoplasm. Particularly, BRCA1 and BRCA2 proteins play a key role in the homologous recombination pathway, and mutations in these genes are associated with more aggressive diseases. The molecular characterization of prostate neoplasm should be routinely integrated into the care of the patients to select who is most likely to benefit from new targeted therapies selectively directed to the use of PARP inhibitors based on the rationale of synthetic lethality. Currently, new concepts (BRACness phenotype, for example) and clinical applications are under development, such as tests that investigate deficiencies in homologous recombination repair genes, among others. Thus, this study reveals the importance of knowing, in a detailed way, the mechanisms of DNA repair and its implication in the clinical practice of the oncologist who assists patients with malignant prostatic neoplasia in its different nuances.

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