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Therapeutic implications of germline vulnerabilities in DNA repair for precision oncology

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A B S T R A C T

DNA repair vulnerabilities are present in a significant proportion of cancers. Specifically, germline alterations in DNA repair not only increase cancer risk but are associated with treatment response and clinical outcomes. The therapeutic landscape of cancer has rapidly evolved with the FDA approval of therapies that specifically target DNA repair vulnerabilities. The clinical success of synthetic lethality between *BRCA* deficiency and poly(ADP-ribose) polymerase (PARP) inhibition has been truly revolutionary. Defective mismatch repair has been validated as a predictor of response to immune checkpoint blockade associated with durable responses and long-term benefit in many cancer patients. Advances in next generation sequencing technologies and their decreasing cost have supported increased genetic profiling of tumors coupled with germline testing of cancer risk genes in patients. The clinical adoption of panel testing for germline assessment in high-risk individuals has generated a plethora of genetic data, particularly on DNA repair genes. Here, we highlight the therapeutic relevance of germline aberrations in DNA repair to identify patients eligible for precision treatments such as PARP inhibitors (PARPis), immune checkpoint blockade, chemotherapy, radiation therapy and combined treatment. We also discuss emerging mechanisms that regulate DNA repair.

Introduction

It is estimated that ~ 5–10% of all cancers are due to pathogenic variants (PV) inherited in the germline.[1] For high-risk families, early identification of a cancer-predisposing germline PV is critical, as subsequent genetic counseling can encourage and motivate patients to adhere to risk-reducing interventions.[1] Germline PVs in DNA repair genes are known to not only increase cancer risk but are also relevant for guiding cancer treatment. DNA repair is crucial for genome stability, with multiple specialized pathways existing in the cell to repair different types of DNA lesions (Fig. 1). These pathways include homologous recombination repair (HRR), non-homologous end-joining (NHEJ), Fanconi anemia (FA), microhomology-mediated end joining (MMEJ), nucleotide excision repair (NER), base excision repair (BER), mismatch

Abbreviations: BC, breast cancer; BER, base excision repair; CRC, colorectal cancer; dMMR, mismatch repair deficiency; DSB, double-strand breaks; FA, Fanconi Anemia; HLRCC, hereditary leiomyomatosis and renal cell cancer; HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; MMEJ, microhomology-mediated end-joining; MMR, mismatch repair; MSI, microsatellite instability; NER, nucleotide excision repair; NHEJ, non-homologous end joining; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor; PC, pancreatic cancer; pCR, pathological complete response; PFS, progression free survival; PV, pathogenic variant; TMB, tumor mutation burden; VUS, variants of uncertain significance.

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repair (MMR), and replication repair.[2]

Tumors with DNA repair defects are particularly sensitive to DNA damaging agents, such as platinum-based chemotherapeutic drugs and radiation therapy. Table 1 shows DNA repair genes that are associated with therapeutic benefit and cancer risk in preclinical and/or clinical studies. In the early 2000s, it was observed that inhibition of PARP in tumor cells, that carry genetic changes damaging *BRCA* (*BRCA1* or *BRCA2*) function, led to synthetic lethality.[3] In 2014, olaparib (Lynparza, AstraZeneca) was the first PARPi that was approved by the Federal Drug Administration (FDA). Olaparib monotherapy was first indicated for advanced ovarian cancer (OC) patients with germline PVs in *BRCA* who had been treated with three or more prior lines of chemotherapy.[4] Since the first approval, the next generation of PARPis (veliparib, niraparib, rucaparib, and talazoparib) have not only demonstrated increase potency but also expanded to the treatment of tumor types that include PVs in other DNA repair genes.[5] Talazoparib (Talzenna, Pfizer Inc.), which is significantly more potent than olaparib, was approved by the FDA on October 16th, 2018 for HER-2 negative locally advanced or metastatic breast cancer (BC) patients with germline PVs in *BRCA*.[6–8] The POLO trial in patients with metastatic pancreatic cancer and the PROfound trial in patients with metastatic castration-resistant prostate cancer led to the approval of olaparib for patients with germline PVs in *BRCA* genes and/or other specific HRR genes respectively.[9–12]

In the last few years, immune checkpoint inhibitors (ICI) have transformed the treatment of solid tumors such as melanoma, lung, head neck, breast, renal, and bladder cancers.[13] Currently, the approved ICIs are monoclonal antibodies targeting programmed cell death protein (PD-1), programmed cell death protein ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) which increase T-cell activation,

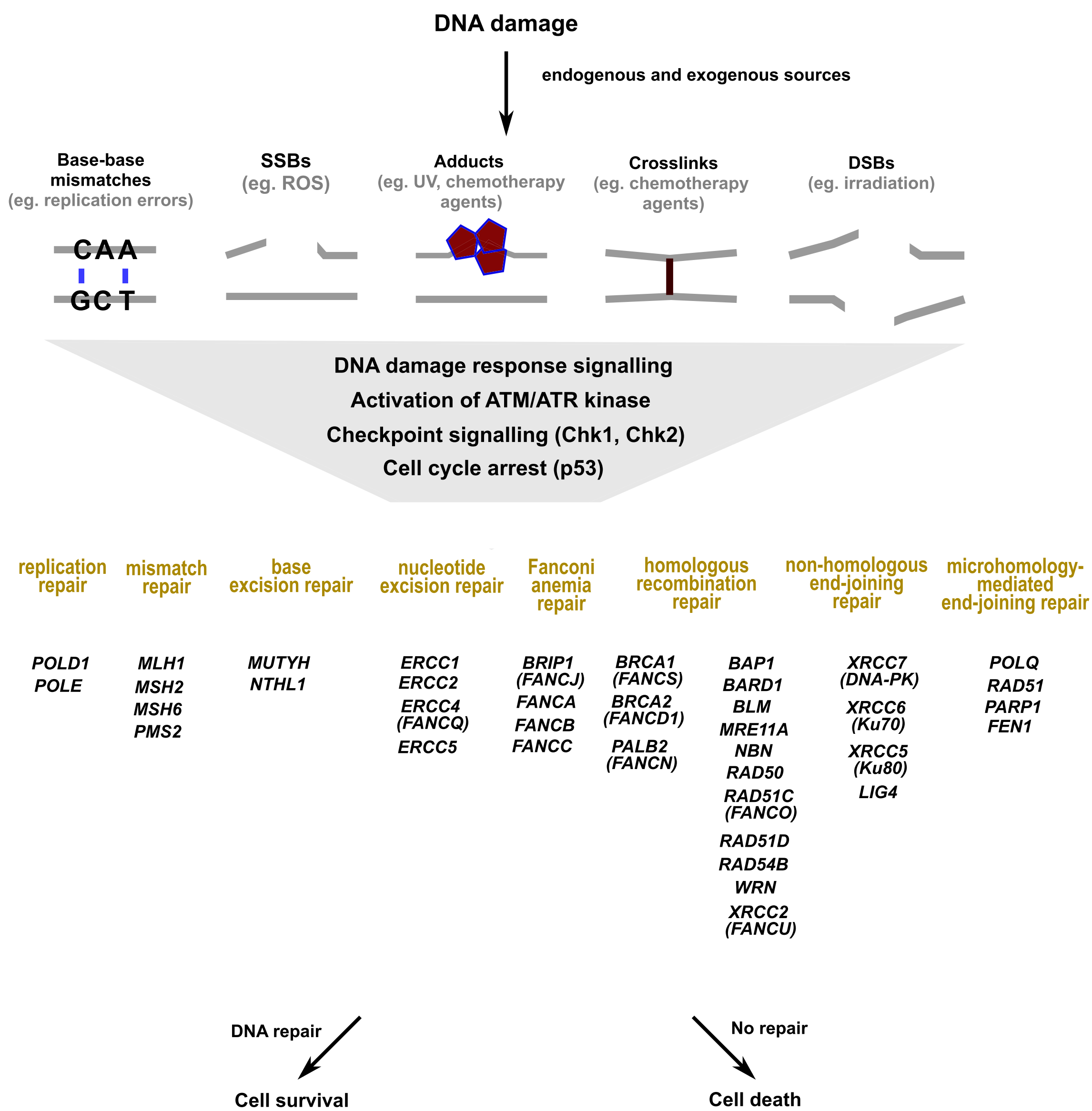

Fig. 1. A simplified view of DNA damage response and repair: cancer risk and approved therapeutic biomarkers or therapies. DNA damage may be caused by multiple endogenous (metabolites, replication errors) or exogenous (irradiation, UV light, chemotherapy agents) sources.[195,196] Multiple forms of DNA damage, such as replication errors, single stranded and double stranded breaks can activate the DNA damage response signaling and the checkpoint response. The DNA damage response signaling involves the activation of the sensory kinases, ATM and ATR. The signals from these sensory kinases are amplified by the checkpoint kinases, Chk1 and Chk2, with cells arresting cell cycle in a p53 dependent manner to either repair the damage or to proceed to cell death via apoptosis.[196–198] Different types of DNA damage are repaired by specialized DNA repair pathways, with pathway members listed below that are associated with increased cancer risk and/or currently tested on germline cancer gene panels. These specialized repair pathways are HRR, FA, MMEJ, and NHEJ for DSBs, BER for single strand breakss, NER for bulky DNA adducts, MMR and replication-repair for base–base mismatches.[197–204]

Table 1
DNA repair genes that are associated with therapeutic benefit and cancer risk in preclinical and/or clinical studies.

Pathway	Gene	Function
BER	*MUTYH*	Excises inappropriately paired adenine bases from DNA backbone to initiate repair[210]
	NTHL1	Releases damaged DNA base from DNA through cleavage of N-glycosidic bond, leaves an AP site [211]
DNA Damage Response	*ARID1A*	Interacts with ATR and recruited to DSBs[179]
	ATM	Associated with sensitivity to DNA damaging agents, ataxia telangiectasia mutated[212]
	BLM	Associated with sensitivity to DNA damaging agents, Bloom syndrome helicase[212]
	CHEK1	Serine/threonine-protein kinase required for checkpoint-mediated cell cycle arrest and activation of DNA repair in response to DNA damage/unreplicated DNA [213]
	CHEK2	Serine/threonine-protein kinase required for checkpoint-mediated cell cycle arrest, activation of DNA repair and apoptosis in response to DNA DSBs[214]
	RECQL4	Associated with sensitivity to DNA damaging agents, Rothmund-Thompson syndrome[212]
	WRN	Werner syndrome helicase / 3′-exonuclease [212]
DNA Replication-Repair	*POLE*	Component of DNA polymerase epsilon complex for leading DNA strand synthesis[215]
	POLD1	Component of DNA polymerase delta complexes for lagging DNA strand synthesis and DNA repair [216]
FA	*BRIP1 (or FANCJ)*	DNA helicase & BRCA1-interacting[212]
	FANCA	Tolerance & repair of DNA crosslinks & other DNA adducts[212]
	FANCB	Tolerance & repair of DNA crosslinks & other DNA adducts[212]
	PALB2 (or FANCN)	Recruit BRCA2 and RAD51 to DNA breaks[217]
HRR	*BAP1*	Promotes DSB repair by interacting with BARD1 [181,182]
	BARD1	E3 ubiquitin-protein ligase[218]
	BRCA1 (or FANCS)	E3 ubiquitin-protein ligase, mediates formation of Lys-6-linked polyubiquitin chains and plays role in repair by facilitating cellular responses to DNA damage[219]
	BRCA2 (or FANCD1)	Binds RAD51, promotes assembly of RAD51 onto single-stranded DNA to potentiate HRR[220]
	MRE11A	3′ exonuclease, defective in ATLD (ataxia-telangiectasia-like disorder)[212]
	NBN	Component of MRN complex which plays critical role in cellular response to DNA damage and maintenance of chromosome integrity[221]
	RAD50	ATPase in complex with MRE11A, NBS1[212]
	RAD51C (FANCO)	Binds single-stranded DNA and double-stranded DNA, DNA-dependent ATPase activity[222]
	RAD51D	Rad51 homolog[212]
	RAD54B	Involved in DNA repair and mitotic recombination[223]
	XRCC2 (or FANCU)	DNA break and crosslink repair[212]
MMR	*MLH1*	Heterodimerizes with PMS2 to form MutL alpha [224]
	MSH2	Forms two different heterodimers: MutS alpha and MutS beta[224]
	MSH6	Heterodimerizes with MSH2 to form MutS alpha [224]
	PMS2	Heterodimerizes with MLH1 to form MutL alpha [224]
NER	*ERCC1*	Structure-specific endonuclease component [225]
	ERCC2	5′ to 3′ DNA helicase[212]
	ERCC4 (or FANCQ)	Structure-specific endonuclease component, removes interstrand cross-link[226]
	ERCC5	Structure-specific DNA endonuclease involved in DNA excision repair, 3′ excision[227]
MMEJ	*POLQ*	DNA polymerase that promotes MMEJ and limits RAD51 accumulation at resected ends[155]
	FEN1	5′ nuclease[212]

AP, apurinic/apyrimidinic site; BER, base excision repair; DSB, double-strand breaks; FA, Fanconi anemia; HRR, homologous recombination repair; MMEJ, microhomology-mediated end joining; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end-joining; pol, polymerase.

proliferation and mount an anti-tumor response.[13] It is well-appreciated that a key biomarker of response to PD-L1 inhibitors is MMR deficiency.[14,15] Notably, tumors with defects in MMR exhibit a high tumor mutation burden (TMB), high neoantigen load, and T-cell infiltration. The cancer agnostic FDA approval of MMR deficiency as a biomarker of PD-L1 inhibitors on May 23rd, 2017 was a landmark decision for treating tumors based solely on the genetic profile regardless of tumor type.[13] Recent studies are finding that other DNA repair defects are also associated with an increased TMB and tumor neoantigen load.[16,17] These findings are paving the way for identifying DNA repair defects that may serve as biomarkers for ICI response.[18] This review will summarize the current literature on DNA repair defects in the germline and their relevance to personalized cancer treatment. In this review, we also discuss emerging paradigms of germline DNA repair vulnerabilities that could be potentially exploited as therapeutic targets. This review does not discuss the biology of the loss of the normal allele in cancer or the nature of the PV (e.g., hyper or hypomorphic alleles), rather focuses on the clinical significance of germline aberrations in specific DNA repair genes as a biomarker for treatment strategies as well as clinical benefit of germline genetic testing for treatment decision.

Germline testing for cancer risk

In 1895, a family was reported with a spectrum of abdominal cancers in different generations, demonstrating a familial predisposition to cancer.[19] In 1985, Dr. Lynch characterized the first of multiple cancer syndromes as Hereditary Non-Polyposis Colorectal Cancer, subsequently designated as Lynch Syndrome.[19,20] Our current understanding of the genetic basis of Lynch Syndrome is due to the groundbreaking research in the 1990s by Bert Vogelstein, Albert de la Chapelle, Manuel Perucho, Fishel Kolodner, and others (extensively reviewed in [20]). It is now well-appreciated that Lynch Syndrome is defined by germline PVs in MMR genes.[21]

In the 1940s, Sir David Smithers noted that BC can cluster in families.[22] In 1990, a large case-control study with 4,730 BC cases and 4,688 matched controls concluded that age of onset was a strong indicator of genetic predisposition to BC.[23] In the early 1990s, Dr. Marie-Clair King's studies linked a region on chromosome 17q21 to increased risk of early-onset BC, identifying *BRCA1*.[24–26] Subsequently, Dr. Michael Stratton linked *BRCA2*, localized to chromosome 13q12-q13, with increased BC risk.[26] Further groundbreaking work, led by multiple groups over several years, confirmed and elucidated that the *BRCA* genes are indeed associated with increased risk of BC and OC.[25–34]

In the early 1990s, *BRCA* gene sequence was commercially patented by Myriad Genetic Laboratories, which then developed and marketed the first widely available commercial DNA sequencing test for hereditary BC and OC risk based on sequencing of *BRCA1*, followed shortly thereafter by the addition of *BRCA2* (the BRCAnalysis test). In 2013, a landmark ruling by the Supreme Court that, 'isolated human genes cannot be patented', rescinded the patents on *BRCA* and this changed the landscape of genetic testing for cancer diagnostics. A period of rapid innovation through next-generation sequencing, the introduction of multiple new commercial entities into the genetic testing marketplace, and expansion of genetic testing criteria followed.[35] It must also be appreciated that the cloning and widescale marketing of *BRCA* testing in the 2000s to evaluate cancer risks in women laid the foundation for enormous growth in the field of clinical cancer genetics. Clinical testing has been proven in this time to not only help guide cancer risk assessment for the carrier and their family members but also in its potential to guide patient management and treatment.[36–38]

Like the *BRCA* genes, multiple other cancer susceptibility genes function in DNA repair pathways (genes in Fig. 1 and Table 1). Today, multigene hereditary cancer panels that include a number of the DNA repair genes listed in Table 1 are used in the clinic to test for germline PVs in cancer susceptibility genes.[36,39–52] An individual with a family history of cancers may undergo germline testing to quantify their cancer risk. If a PV is found in an individual, their physician(s) can perform cancer screening for early detection, develop preventive management plans, or prevention procedures; or patients may personally maintain their health through behavioral modification and risk mitigation. The results of germline testing may also guide patient treatment.[53] Perhaps equally important, the identification of a PV can motivate family members to undergo testing for cancer risk assessment and risk stratification.[8,53,54]

Patients are selected for genetic testing based on personal and family cancer history, the assessment of which has been codified in numerous practice guidelines. However, there is increasing evidence to suggest that germline sequencing may also be beneficial for patients who do not meet guidelines for genetic testing. Advanced stage (stage III-IV) cancer patients (n = 1040) were sequenced for 76 cancer predisposition genes and ~ 17.5% of these patients (182/1040) had clinically actionable germline PVs in cancer risk genes.[55] Among the 17.5% patients with germline PVs, over half (~9.7%, 101/1040) did not meet clinical criteria for testing, and these PVs would not have been detected based on the current guidelines. In pediatric cancer patients (n = 1120), it was found that ~ 8.5% had a PV or a likely PV.[56] Here, only 40% of the pediatric patients with cancer-predisposing PVs had a family history of cancer. Analysis of whole-exome data from 49,738 participants in the UK Biobank found that ~ 1% (441/49738) of the cohort harbored PVs in genes associated with familial hypercholesterolemia, hereditary breast and ovarian cancer syndrome, and Lynch syndrome. These individuals in the cohort with the PVs (or likely PVs) were at increased risk for the associated diseases and were not reliably detected by their family history alone.[57] Germline testing in a prospective cohort of patients with solid tumors found that multigene panel testing identified PVs in 13.3% (397/2,984) of the patients. Here, treatment strategies were modified for 28.2% (42/397) of the patients based on the germline findings.[58] Manickam et. al. found that exome sequencing based screening strategies identify 5 times as many individuals with *BRCA* GPVs than screening based on family history.[59] Beitsch et. al. found that testing based on current guidelines misses nearly half of the BC patients with a GPV.[60]

Although the current literature suggests benefit of population-based screening, there are several barriers to genetic testing such as lack of initial referral from the oncologist, poor knowledge of genetics, access to care, health insurance, medical costs, and confidentiality concerns.[61–63] Recent studies are focusing on understanding and addressing these barriers so that more patients can benefit from genetic testing.[62,63] In conclusion, the increased utilization of next-generation sequencing technology in the clinic, significant reduction in the cost, and broader community acceptance have made it possible to identify clinically actionable germline PVs.[57,58,64,65]

Interpretation of germline variants

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology have established guidelines for the classification of variants identified through clinical genetic testing further grounding the wide applicability of cancer risk assessment. Variants are classified under five categories of increasing disease severity: benign, likely benign, variants of uncertain significance (VUS), likely pathogenic, and pathogenic.[66] Clinical testing has identified a huge number of rare variants that are currently classified as VUS, and it is not known whether these impact cancer risk.[66] For example, while the clinical significance of a germline PV in an MMR gene is straightforward, the interpretation of clinical significance is not straightforward when a patient harbors a germline VUS in an MMR gene. These VUS account for ~ 20–30% of variants in MMR genes.[67] Thus, a critical aspect in the field of cancer risk and treatment decision is to evaluate the clinical significance of VUS in DNA repair genes.

The interpretation of VUS is challenging and inclusion of multiple lines of evidence has been suggested, for example, the inclusion of data such as presence in the general population (rare variants with minor allele frequency < 1%), segregation of the variant with the disease, *in silico* prediction of variant effect as predicted-pathogenic or predicted likely-pathogenic, results from structural modeling, mutation rates, and signatures in the tumor, biochemical assays of the variant.[67] As PVs in MMR and DNA polymerase genes are known to be associated with increased mutation rates, the analysis of tumor sequence data has become increasingly important when a VUS is found in these genes.[68] Intriguingly, primary lymphocytes from familial early-onset cancer patients, that carried predicted-pathogenic germline variants in DNA repair genes, exhibited a constitutional defect in the suppression of double strand breaks (DSBs).[69,70] These results suggest functional assays in primary lymphocytes may assist in providing the various lines of evidence required to clinically interpret the relevance of specific germline VUS in DNA repair genes.

Overall, knowing that a variant is indeed a PV or is benign may aid clinicians in interpreting results from germline testing and guiding patients for their cancer risk as well as personalized treatment.[67] Recent studies suggest implementation of multidisciplinary molecular tumor board teams to recommend customized therapeutic solution(s) for cancer patients that have failed existing treatment.[71,72] The multidisciplinary team recommends therapeutic strategies based on a comprehensive integrated review of results from genetic testing (germline and/or somatic, TMB etc.), other laboratory results (imaging, pathology, biomarker etc.), patient's clinical and family history along with potentially available clinical trials.[71,72] Kato and colleagues showed that patients who received molecular tumor board recommended treatment had better clinical outcomes.[73] Currently, there is a need for global standardization of molecular tumor boards to deliver therapeutic recommendations that can facilitate the goals of precision oncology.[71,74]

Therapeutic implications for ICIs

Conventionally, the knowledge of germline PVs in DNA repair genes has informed our understanding of cancer risk. More recently, DNA repair pathways have emerged as playing a major role in the selection of patients for ICI therapy. In 2017, the PD-1 inhibitor pembrolizumab received FDA approval for adult and pediatric patients with metastatic or unresectable tumors with microsatellite instability-high (MSI-H) or MMR deficiency (dMMR) phenotype that has progressed following previous treatments or for whom no other treatment options are available. Five studies contributed data for the FDA application, with a total of 149 patients that had MSI-H or dMMR tumors.[75–77] Of the 149 patients, 90 patients had metastatic CRC, and 59 patients had other cancers. Further, out of the 149 patients, 59 patients responded to treatment (objective response rate (ORR) = 39.6%, 95% CI, 31.7–47.9), with a 7% complete response rate.[75–77]

The landmark tumor agnostic FDA approval of pembrolizumab was based on the understanding of the biology of dMMR/MSI-H which occurs due to germline or somatic PVs in MMR genes (*MLH1*, *MSH2, MSH6*, *PMS2*). The MMR proteins maintain genome stability by correcting single base nucleotide insertions or deletions.[78] Germline PVs impairing MMR are associated with the autosomal dominant condition, Lynch Syndrome, which increases the risk of CRC, endometrial cancer, and several other cancers, such as OC, brain, skin, pancreatic, and other gastrointestinal cancers.[79,80] Currently, ~1–7% of CRCs, and ~ 13–25% of endometrial cancers are associated with germline PVs in MMR genes.[81–83] Somatic PVs in MMR are also common in tumors; for example, in ~ 12–15% of localized CRC, ~3–4% of metastatic CRC, and up to 25% of endometrial cancers.[80,84,85] Epigenetic silencing of the *MLH1* promoter due to hypermethylation can also contribute to dMMR tumors.[86,87] Other sources of dMMR include deletions at the 3′ end of *EPCAM* which causes the inactivation of the nearby *MSH2* gene.[86] Although rare, it is also possible to inherit two MMR variants (one from each parent), which can result in either a compound heterozygote or, if the variants are in the same MMR gene, a rare recessive inherited syndrome known as Constitutional MMR Deficiency leading to a wide spectrum of childhood malignancies.[78] In a case study, two siblings with consitutional dMMR and recurrent glioblastoma were treated with PD-1 inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) which led to a significant clinical benefit.[88] Recently, anti-PD-1 monoclonal antibody, dostarlimab (Jemperli, GlaxoSmithKline) showed clinical benefit in patients with dMMR endometrial cancer.[89,90] Based on the results of the GARNET trial, dostarlimab was approved by the FDA for patients with recurrent or advanced dMMR endometrial cancer[89,90].

It is well-appreciated that dMMR leads to increased TMB and tumor neoantigen production, potentially contributing to the better response to ICIs.[91–93] Infact, testing for dMMR or MSI-H also can identify patients with TMB-H. In June 2020, accelerated FDA approval for pembrolizumab was indicated for the treatment of TMB-high (or TMB-H, ≥10 mutations/megabase) adult and pediatric unresectable or metastatic tumors that have either progressed on prior therapy or for which no other treatment options are available.[94] Germline PVs in DNA polymerase genes, *POLE* (typically in exonuclease domain) and *POLD1*, increase the risk of CRCs, endometrial cancers, OC, other malignancies, and have been associated with ultra-hypermutation in the tumor (i.e. tumors with > 100 mutations/megabase).[68,95–97] Latest data suggest that germline PVs in *POLE* and *POLD1* lead to ~ 0.1–0.4% of familial cancers.[68,98] While several studies have focused on variants in the exonuclease domain, increased TMBs have also been noted with variants outside the exonuclease domain.[99,100] Patients with *POLE/POLD1* variants had significantly better clinical outcomes following treatment with ICIs when compared to patients without them.[101,102] No difference in clinical outcomes was observed in patients with *POLE/POLD1* variants in the exonuclease domain or outside the exonuclease domain.[102]

Several trials are underway to determine the efficacy of ICIs in combination with PARPis (**Supplemental Table 1**).[103,104] The rationale for this combination arises from the observations that PARP inhibition increases DNA damage, which is particularly pronounced in cells that carry DNA repair defects such as *BRCA* deficiency. This damage not only leads to increased priming of the immune system in the tumor microenvironment but also increases the tumor intrinsic immunogenicity by modulating the expression of surface markers such as PD-L1 (reviewed in [105]). In models of small cell lung cancer, it was shown that PARP (and Chk1) inhibition leads to a strong anti-tumor immune response by recruitment of cytotoxic T-lymphocytes via the activation of the STING pathway.[106] Based on these observations, an ongoing non-interventional, prospective clinical study (NCT03495544, **Supplemental Table 1**) is evaluating the association between germline PVs in hereditary BC genes (such as *BRCA1, BRCA2, CHEK2*) and PD-L1 expression in breast tumor cells and immune cells. This study will evaluate the relationship between germline PVs, and PD-L1 expression to allow precision selection of ICIs in these patients. Interestingly, a recent preclinical study showed that *BRCA* deficiency differentially modulates the tumor microenvironment.[107] While *BRCA1* mutations may drive immune responses that limit benefit from ICI, *BRCA2* mutations increased tumor immunogenicity and showed benefit from ICI therapy.[107] These observations suggest a mechanistic difference between the *BRCA* genes and warrant further investigation.[107]

Therapeutic implications for PARPi therapy

PARPis prevent the repair of single-strand breaks, and in HRR-deficient cells these single strand breaks are converted to DSBs which ultimately lead to unrepaired damage and consequent cell death.[108–110] Proof-of-concept studies in 2005 and 2007 provided the rationale for the use of PARPis in cancer therapy.[4,111] In 2009, a phase I trial evaluated the antitumor activity of the PARPi, olaparib, for cancer patients with either wild-type or BRCA (*BRCA1* or *BRCA2)* PVs.[112] In the expansion phase of the trial, only *BRCA* (*BRCA1* or *BRCA2*) PV carriers with OC, BC, and prostate cancer were enrolled and these patients showed clinical benefit from olaparib.[112] In 2014, olaparib monotherapy received FDA approval for advanced OC patients with a germline PV in *BRCA* who have had three or more lines of prior chemotherapy.[4]

The efficacy and tolerability of olaparib in advanced OC and BC patients with germline *BRCA* PVs were assessed in two proofs-of-concept multicenter phase II studies.[113–116] In 2018, the FDA approved olaparib therapy for patients with germline *BRCA* PVs in HER2-negative metastatic BC patients based on the results from the OlympiAD trial (**Supplemental Table 2**).[54,116,117] While no statistically significant change or improvement in median overall survival (OS) was observed, an OS benefit was observed in patients who had not previously been treated for metastatic BC (hazard ratio: 0.51, 95% CI, 0.29–0.90).[118] Overall, treatment with olaparib significantly increased the ORR and OS of the metastatic BC patients. A pooled analysis was performed to explore the benefit of olaparib in OC patients carrying germline PVs in *BRCA* who had received multiple lines of prior chemotherapy. Here, all patients had received olaparib monotherapy at relapse, and 91% (273/300) patients were evaluated for response.[119] In the pooled analysis, the ORR was 36% (95% CI, 30–42) and the median duration of response was 7.4 months (95% CI, 5.7–9.1).[112] In the subset of patients with measurable disease at baseline (205/300) who had received ≥ 3 lines of prior chemotherapy, the ORR was 31% (95% CI, 25–38) and median duration of response was 7.8 months (95% CI, 5.6–9.5). This analysis demonstrated that olaparib monotherapy was safe and effective not only for patients at baseline but also for the patients who underwent multiple prior chemotherapies (both platinum-sensitive and resistant).[119] In Study 19, a phase II trial of olaparib maintenance monotherapy in relapsed OC patients (n = 265) with *BRCA* PVs (germline or somatic), olaparib-treated patients had a higher PFS when compared to the patients in the placebo arm (median, 8.4 months vs. 4.8 months; $P < 0.00001$).[120] A retrospective analysis of these patients found that the benefit of olaparib versus placebo was greater in patients with *BRCA* PV when compared to patients without *BRCA* PVs.[120]

The PROfound trial in metastatic castration-resistant prostate cancer patients with specific HRR gene PVs evaluated their response to olaparib.[11,12,121] ORR was 33% (n = 16/49; 95% Cl, 20% to 48%), and homozygous and/or deleterious somatic or germline aberrations in *BRCA, ATM, FANCA*, and *CHEK2* were identified in 16 out of 49 (33%) patients.[121] The POLO trial assessed the efficacy of olaparib maintenance therapy in metastatic pancreatic cancer patients with germline *BRCA* PVs.[9] This trial showed that the olaparib maintenance therapy can extend PFS in metastatic pancreatic cancer patients.[9] Recently, two parallel phase II studies concluded that olaparib may be therapeutically efficacious for pretreated advanced pancreatic cancer patients with PVs in other DNA repair genes (**Supplemental Table 2**).[122]

Following the success of olaparib, several next generation PARPis have also received FDA approval including veliparib, niraparib, rucaparib, and talazoparib. Mechanistic studies have increased our understanding of how PARPis exert their anti-cancer activities (Fig. 2), however, this is still not completely understood. Initially, PARPis were thought to exert anti-tumor activity by inhibiting the catalytic activity of PARP1/2.[5,123] Subsequently, it was shown that PARPis effectively 'trap' the PARP1- and PARP2- DNA complexes in pre-clinical testing (Fig. 2).[5] Olaparib, veliparib, niraparib, rucaparib, and talazoparib all have been shown to have PARP-trapping activity.[5] Mechanistically, these inhibitors function similarly, however it has been shown in biochemical assays that veliparib functions as a catalytic inhibitor with slight trapping activity, while olaparib, niraparib and rucaparib function as PARP trappers, ~100-fold more efficiently in comparison to veliparib (Fig. 2).[5,123] Talazoparib is by the far the most potent PARP trapper with ~ 100-fold more PARP-trapping efficiency than olaparib, rucaparib, and niraparib (Fig. 2).[5,123] Both olaparib and rucaparib (Rubraca, Clovis Oncology) have been approved for treatment-refractory OCs with germline *BRCA* PVs. Niraparib (Zejula, GlaxoSmithKline) and olaparib have both received FDA-approval for maintenance therapy in patients with recurrent OC.[124,125] Niraparib was approved for women with recurrent OC in March 2017, for late-line treatment of women with recurrent OC in October 2019, and as the first-line maintenance monotherapy in April 2020 for women with advanced OC regardless of biomarker status (PRIMA trial).[126] In the PRIMA trial, newly diagnosed advanced OC patients were matched to either niraparib or the placebo. A statistically significant PFS improvement and higher OS in the niraparib cohort were observed compared to the placebo, regardless of HRR deficiency status.[126,127]

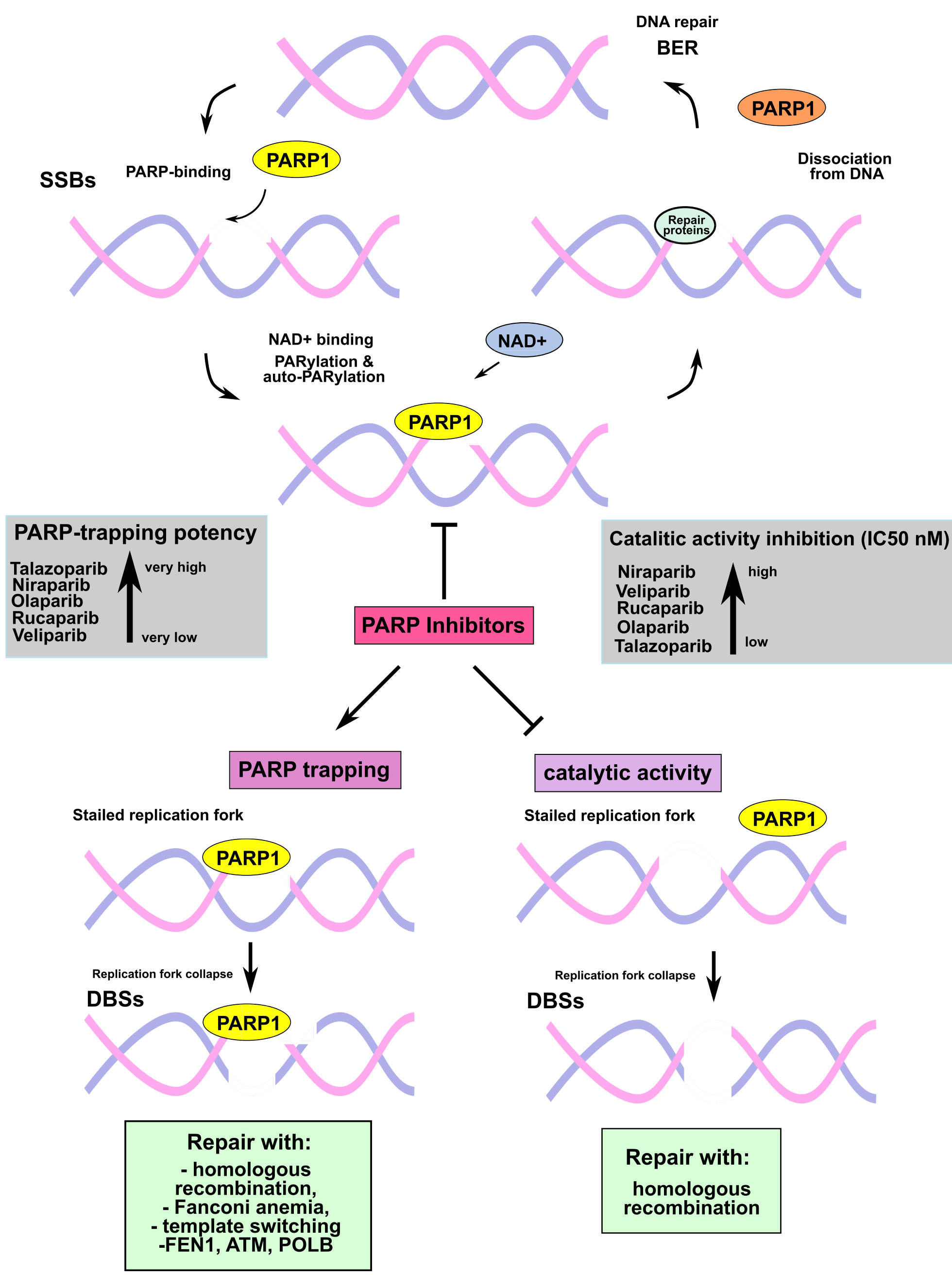

Fig. 2. A simplified view of PARP1 function in DNA damage response and PARP1 inhibition mechanisms. When a single-strand break occurs, PARP1 binds to the damaged site and uses NAD + as a substrate for PARylation and auto-PARylation. PARylation leads to the recruitment of DNA repair proteins, and auto-PARylation decreases the affinity of PARP1 to DNA. PARP1 dissociates from DNA and BER proteins repair DNA. PARPis differ significantly in their ability to trap PARP1 and/or inhibition of PARP1 catalytic activity.[205,206] There are two known mechanisms of PARP1-inhibition, PARP1-trapping (left) and inhibition of PARP1 catalytic activity (right). During PARP1 trapping, the PARPi binds directly to the PARP1 active site, and prevents dissociation of PARP1 from DNA, leading to replication fork stalling and DSBs.[205] Here, the DNA damage might be repaired via HRR, FA, template switching, and other repair proteins.[207,208] In the second mechanism, the binding of NAD + to PARP1 is prevented and thereby PARP1 loses the ability to use its substrate and perform catalysis with downstream replication fork staling and DSBs.[207,209] Here, the DNA damage might be repaired via HRR.[207,208]

The BrighTNess trial assessed the addition of PARPi, veliparib, plus carboplatin to standard neoadjuvant paclitaxel chemotherapy or carboplatin alone to standard neoadjuvant chemotherapy in stage II-III triple-negative BC patients (n = 634) (**Supplemental Table 2**).[38] The pathological complete response (pCR) was higher in patients that received the combination of veliparib, carboplatin, and paclitaxel (53%, n = 68/316) versus the patients that received paclitaxel alone (31%, n = 49/158), but not higher when compared to the group that received carboplatin alone with paclitaxel (58%, n = 92/160).[38] Here, 51% of the patients (47/92) with a germline *BRCA* PV achieved a pCR versus 48% of the patients (262/542) without a germline *BRCA* PV that achieved a pCR.[38] In the GeparOla trial, early HER-2 negative breast cancer patients with HRR deficiency (germline or somatic *BRCA1* or *BRCA2* PV and/or HRR deficiency) received either paclitaxel plus olaparib with standard chemotherapy or paclitaxel alone with standard chemotherapy. The addition of olaparib with paclitaxel showed a significantly higher rate of pCR in hormone receptor-positive patients that were < 40 years of age, warranting further investigation in primary BCs.[128] Ongoing trials (NCT02227082, NCT01562210, NCT02229656, **Supplemental Table 2**) are assessing PARPis as radiosensitizers and assessing the safety and tolerability of the combination treatment.

Several trials are assessing the activity of PARPis in tumors with mutations in other DNA repair genes.[129–132] Yurgelun et al. showed that pancreatic ductal adenocarcinoma patients with germline PVs in other HRR genes had a better OS when compared to patients without them.[133] A phase II trial (NCT04508803, **Supplemental Table 2**) is assessing the combination of an anti-PD1 monoclonal antibody, HX008, in combination with the PARPi, niraparib in metastatic BC patients with germline PVs in multiple DNA repair genes apart from *BRCA*. Another phase II, interventional trial (NCT03967938, **Supplemental Table 2**) is assessing the efficacy of olaparib in advanced cancer patients with germline or somatic PVs in HRR genes. With the availability of germline multigene panel data from cancer patients, several studies are finding that germline PVs in DNA repair genes are overrepresented in cancers where the use of PARPis has not been established.[134–136]

While PARPi therapy has been revolutionary, *de novo* or acquired resistance to PARPi has been observed in patients. Several mechanisms have been proposed such as alterations in PARP1 leading to increase in PARP1 catalytic activity or removal of PARP trapping, restoration of HRR via *BRCA* reversion mutations or demethylation of BRCA promoter as reviewed by Lee and Matulonis.[137] It is anticipated that the number of patients that are resistant to PARPis will continue to rise and thus it is critical to understand the mechanisms of PARPi resistance for optimizing treatment strategies such as targeted combination therapy.[137] In summary, several PARPis have been approved as therapeutic and maintenance therapy for multiple cancer types, typically based on the presence of germline or somatic *BRCA* PVs. Furthermore, PARPi therapy is currently being investigated in patients with alterations in other DNA repair genes and combination with other treatments so that a broader range of patients can achieve clinical benefit.

Implications for chemotherapy and radiation therapy

It is now well-appreciated that *BRCA* deficiency can increase sensitivity to DNA crosslinking agents (such as platinum-based agents) and ionizing radiation.[138] In 2010, a pilot study assessed a small group of women (n = 12) with BC and a germline *BRCA1* PV.[139] Here, 10 of the 12 (~83%) women had a pCR to neoadjuvant cisplatin. These findings were validated in a larger study in 2014 in women with early-stage BC and a *BRCA1* germline PV. Here, 61% of the women experienced a pCR to the neoadjuvant cisplatin.[139] In a phase II trial, patients (n = 28) with stage II and stage III triple-negative BC were treated with neoadjuvant cisplatin. Then, after undergoing definitive surgery, these patients received standard adjuvant chemotherapy and radiation therapy. Here, 22% (6/28) of the patients experienced a pCR. Interestingly, of the 6 patients with pCR, only 2 patients had a germline *BRCA1* PV. Additionally, 64% of patients had a complete or partial response. These studies showed that while patients with a germline *BRCA1* PV have a good response to cisplatin, there is a subset of patients with wild-type *BRCA1* and triple negative BC that also respond to cisplatin.[140] In a phase II non-randomized trial, women with metastatic BC and a germline *BRCA1* PV were treated with cisplatin chemotherapy. An ORR of 80% (16/20) was observed, with 45% (9/20) of the patients exhibiting complete clinical response, and 7/20 (35%) patients exhibited a partial response.[141] This study demonstrated that cisplatin was highly effective in women with metastatic BC and *BRCA1* PVs.

The INFORM trial prospectively assessed pCR in newly diagnosed HER2-negative BC patients with germline *BRCA* PVs with neoadjuvant cisplatin versus anthracycline-based therapy (**Supplemental Table 3**). The study patients were randomly assigned to neoadjuvant single-agent cisplatin or to doxorubicin-cyclophosphamide.[142] The pCR rates for neoadjuvant cisplatin and doxorubicin-cyclophosphamide were 18% and 26% respectively. This study did not find any differences in pCR and residual cancer burden by either agent in patients with triple negative BC, consistent with those reported by the BrighTNess and Geparsixto trials.[38,142,143] The results from the INFORM trial suggest that *BRCA* PV status might predict sensitivity to any DNA damaging agents and not exclusively to platinum-based agents. Recently, a small trial of neoadjuvant talazoparib without chemotherapy reported a pCR of 53% in 20 patients with operable BC and a germline PV in *BRCA*, warranting larger investigation including comparison with neoadjuvant chemotherapy.[144]

A 2006 retrospective study compared the outcomes in BC patients with germline *BRCA* PVs to patients with sporadic BC. All patients in the study had breast conservation surgery and received radiation therapy for their stage I or II BC with no significant differences observed in in-breast tumor recurrence in the carriers versus the non-carriers. This study also did not find any significant difference in recurrence in the carriers versus the non-carriers who underwent bilateral oophorectomy. However, the recurrence rates were twice as high in the carriers who did not undergo oophorectomy. Also, as expected, the study found an increased incidence of contralateral BCs in the carriers versus the non-carriers. While tamoxifen significantly reduced the incidence of contralateral BCs in carriers, the incidence remained higher than sporadic non-carriers.[145] Overall, this study suggests that hormonal intervention and prophylactic bilateral oophorectomy are associated with reduced recurrence or reduced risk of new primary BCs and fewer contralateral BCs in carriers. Despite this, carriers still have a high risk of contralateral BCs, warranting the need for additional strategies in carriers undergoing breast conservation surgery to reduce their risk. A prospective study found that an equal proportion of carriers chose breast conservation surgery and bilateral prophylactic mastectomy for risk reduction, thus warranting assessment of additional risk-reduction strategies for breast conservation surgery.[144]

Beyond BC, women with OC who are carriers of a germline *BRCA1* or *BRCA2* PV have also shown high response rates to platinum-based therapy. In a study by Gorodnova et al., 34 *BRCA1* and 1 *BRCA2* germline PV carriers were identified. The total clinical response in the patients with germline PVs in *BRCA* to platinum-based therapy was determined to be 34% (n = 12/35). In contrast, the clinical response rate of the patients with somatic PVs in *BRCA* was determined to be 4% (8/190).[146] In a retrospective study, men with castration-resistant prostate cancer, with or without germline *BRCA2* PVs, were assessed for response to platinum-based therapy. These patients were treated with carboplatin and docetaxel and were categorized based on the germline *BRCA2* PV status. This study found a significant association between the germline *BRCA2* PV status and the response to platinum-based therapy.[147] Overall, both chemotherapy and radiation therapy act by inducing DNA damage, and vulnerabilities in DNA repair, either germline or somatic, impacts response to these therapies.

Therapeutic implications of germline variants in other DNA repair genes

Growing evidence suggests that germline variants in other DNA repair genes may also impact response to cancer therapeutics. Defects in the Fanconi Anemia (FA) pathway lead to impaired ability to perform homology-directed repair and thereby increased sensitivity to DNA cross-linking agents.[148] Tumors carrying germline defects in the FA are also sensitive to PARPis.[148] There are 22 FA or FA-like genes including *FANCA, B, C, D1* (or *BRCA2*)*, D2, E, F, G, I, J* (or *BRIP1*)*, L, M, N (or PALB2), O* (or *RAD51C*)*, P* (*or SLX4*), *Q* (or *ERCC4*), *R, S* (or *BRCA1*)*, T* (or *UBE2T*)*, U* (or *XRCC2*)*, V* (or *REV7*) and *W* (or *RFWD3*).[149–151] The *BRCA* genes and several associated HRR genes are important members of the FA pathway. FANCD2-FANCI monoubiquitinylation is a critical step in the activation of the FA pathway and can be assessed by nuclear staining of monoubiquitylated FANCD2.[152] In non-small cell lung cancer, it was observed that a subset of tumors was negative for FANCD2 foci staining (22%, n = 23/104) and thus was considered deficient in FA pathway.[148] These results suggest that at least a subset of lung cancers may be sensitive to DNA damaging therapy and/or PARPi therapy due to their limited ability to perform FA repair.[148] In a clinical study, 643 tumors (including BC, OC, CRC, endometrial, lung, and several other cancers) were evaluated for FANCD2 nuclear foci and 28.7% (185/643) were found to be negative.[153] Here, 61 patients with FANCD2-foci negative tumors received either veliparib alone or in combination with mitomycin C, and 6 patients in the combination arm showed clinical benefit. Subsequent tumor sequencing found germline alterations in the FA pathway. These data suggest that PARPi alone or in combination with a DNA damaging therapy is safe and can lead to clinical benefit in some patients with FA-deficient tumors.[153]

The MMEJ pathway is emerging as a promising therapeutic target; it begins after exposure of microhomology (i.e., short complementary sequence) regions for alignment of DNA ends.[154] Following the alignment, the resulting 5′ flaps are processed, the gaps are filled by a polymerase and then ligated. PARP1 is an essential component of the MMEJ pathway and PARPi can also inhibit the MMEJ pathway.[154] Furthermore, loss of expression of MMEJ proteins such as POLQ and FEN1 in HRR-deficient cells was found to cause synthetic lethality.[154,155] While MMEJ pathway is emerging as a promising biomarker to guide cancer treatment, only the therapeutic potential of somatic tumor alterations has been assessed so far. Brandalize et. al. identified a germline polymorphism in the promoter region of *POLQ* that was associated with increased risk of inherited BC, warranting further studies on cancer risk and therapy outcomes.[156]

The core NER genes include *ERCC1, 2 (XPD), 3 (XPB), 4 (XPF), 5 (XPG), 6 (CSB), 8 (CSA), XPA, XPC, TFIIH, LIG1, RPA,* and *DDB1*.[157] The NER pathway excises bulky DNA lesions such as those generated by platinum-based agents.[158] Targeting the core NER protein complex, the ERCC1-ERCC4 heterodimer has been shown to improve cisplatin cytotoxicity in several cancer cell line models.[159] Additionally, it has also been suggested that low nuclear ERCC1 expression may correlate with improved treatment response and confer sensitivity to radiation therapy in head and neck cancer.[160] A *meta*-analysis of 836 non-small cell lung cancer patients found that ERCC1 protein levels could predict better PFS and OS to platinum-based therapy.[158,161,162] Three regulatory polymorphisms in NER genes were determined to predict better PFS and OS following treatment with cisplatin.[158] NER genes were also shown to be differentially expressed in CRC and normal colon tissues, with the expression of *ERCC2, ERCC4*, and *XPC* associated with CRC prognosis.[163] Aiello et al. evaluated *ERCC1* T19007C and C8092A SNPs in tumor specimens from two independent cohorts of lung cancer patients who had received nivolumab. Here, a better response to nivolumab was observed in patients with *ERCC1* C8092A SNP.[164] Overall, preclinical studies suggest that defects in several DNA repair genes could potentially predict response to therapy, however it remains to be determined how effective they are for patient stratification.

Therapeutic implications of germline variants in genes that regulate DNA repair

Several genes that do not directly mediate DNA repair are emerging as key regulators of DNA repair pathways. Recent work is defining the molecular circuits that govern the relationship between androgen receptor signaling and DNA repair.[165,166] Combined therapy of androgen deprivation and radiation has been the standard treatment for prostate cancers showing improved outcomes for high-risk prostate cancer patients.[167–169] Previously, the mechanisms that led to this outcome benefit were not known. It was recently shown that androgen receptor activity is induced by DNA damage, and in turn, promotes transcription of DNA repair genes.[165,166] Intriguingly, patients at a high risk for familial prostate cancer frequently carry germline variants in DNA repair and androgen receptor signaling genes and function-testing of their primary lymphocytes showed increased sensitivity to DNA damaging agents.[70]

VHL germline PVs cause Von Hippel-Lindau syndrome and strongly predispose individuals to renal cancer.[170–172] It is appreciated that VHL is important for the ubiquitination and proteasomal degradation of hypoxia-inducible factor-alpha (HIF1-alpha and HIF-2alpha). Inactivation or loss of *VHL* leads to the constitutive expression of HIFalpha, which freely translocates to the nucleus and activates the expression of multiple genes that are relevant for tumorigenesis. Interestingly, several DNA repair genes, including HRR and MMR, are down-regulated during hypoxic stress.[173–175] In fact, hypoxia has been specifically shown to downregulate the expression of *BRCA1* and *RAD50*, which are critical for HRR.[176,177] Investigation of *VHL*-deficient renal cancer cell lines (786-O, RCC4) found reduced expression of HRR and MMR genes, the persistence of radiation-induced DSBs, and increased sensitivity to PARPis.[178]

ARID1A and *BAP1* are tumor suppressor genes, and their protein products play important roles in DNA repair.[179,180] ARID1A is recruited to DSB sites via an interaction with DNA damage response signaling kinase ATR. Studies in both *in vitro* and *in vivo* models of cancer have shown that ARID1A deficiency sensitizes cells to PARPis.[179] BAP1 interacts with BARD1 and promotes HRR to repair DSBs.[181,182] No known therapeutics that exploit *ARID1A* deficiency have been discovered. However, phase II trials focusing on the effect of PARPis on patients with *BAP1* PVs are underway (NCT03207347) alongside mechanistic studies that focus on the specific nuclear processes that involve *BAP1*.[181,183] Several other clinical trials (NCT03425201, NCT03207347, NCT03786796, NCT03741426, NCT03682289, NCT04068831, NCT03875313, NCT03729245, NCT04195750) are also currently underway to test a combination of PARPis with other treatment strategies in renal cancer.[180]

Germline PVs in the citric acid cycle genes *FH* and *SDHx* are associated with cancer predisposition syndromes.[184–187] Heterozygous loss-of-function PVs in *FH* are associated with hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome and these patients are predisposed to aggressive papillary renal cell carcinoma which are refractory to standard therapies.[186] Similarly, heterozygous loss-of-function PVs in *SDHx* (*SDHA, SDHB, SDHC, SDHD*) are associated with *SDH*-related hereditary paraganglioma and pheochromocytoma (SDH PGL/PCC). Patients with certain familial renal cancers, and familial gastrointestinal stromal tumors also harbor germline PVs in *FH* and *SDH*x.[134,188,189] Loss of FH and SDH function leads to the cellular accumulation of metabolites, with fumarate observed in patients with HLRCC syndrome and succinate in patients with SDH-PGL/PCC.[187] Sulkowski et. al. found that primary tumors from HLRCC and SDH PGL/PCC patients showed elevated DSBs. They also showed that fumarate or succinate can competitively inhibit lysine demethylases KDM4A and KDM4B due to structural similarities. KDM4A and B are important regulators of DNA repair, specifically the repair of DSBs by HRR.[187] *In* *vitro* assessment in HEK293FT renal cells showed that deregulation of *SDHB* and *FH* led to the accumulation of metabolites and DSBs. Downregulation of *SDHB* or *FH* conferred increased sensitivity to DNA damaging therapies and PARPis in preclinical studies. Overall, this is an exciting new area of crosstalk between metabolism and DNA repair, and germline defects in these genes could be relevant for response to therapies that target DNA repair.

Finally, regulation of histone modifications is essential for genomic stability and this process is often aberrant in multiple cancers.[190] Several lysine demethylase inhibitors are being developed as potential agents to enhance response to radiotherapy or genotoxic chemotherapy.[191] The lysine methylation modifications regulate gene expression based on the position of methylation and methylation state.[192] For example, methylations in H3K4, H3K36, and H3K79 are generally associated with active transcription, while methylations in H3K9, H3K27, and K4K20 are associated with repressed transcription. These lysine methylations are regulated by histone methyltransferases and demethylases; defects in these have been associated with several diseases. [192] The pattern of histone methylations not only serves as a focal point for DSB repair proteins (such as HRR and NHEJ proteins) to assemble but also selects the pathway to repair the DSBs.[193] For example, H3K9 demethylases remove repressive H3K9 methylations and have been shown to play a role in DSB repair.[191] Some H3K9 demethylases (such as JMJD1A, PHF2) upregulate the expression of DNA repair factors involved in HRR and/or NHEJ. Other H3K9 demethylases (such as JMJD1C, KDM4D, PHF8) directly regulate DSB repair by migrating to the lesion and regulating the recruitment or function of DSB repair factors.[191] While some H3K9 demethylases (KDM4D, PHF8) are required for DSB repair, their precise mechanism with which they alter DNA repair has not been clearly defined.[191] Currently, it is not known how germline variants in core histone proteins may impact DNA repair and response to DNA damaging therapies.[194]

Conclusions

The massive use of next-generation sequencing technology in the clinic has revealed a rich landscape of germline defects in DNA repair genes. The availability of FDA-approved therapies that specifically target DNA repair defects such as PARPis or ICIs that show benefit in patients with DNA repair defects have expanded the clinical options for cancer patients with durable responses and long-term benefits. Given the significance of DNA repair defects for cancer risk and treatment response, it is important in the future to determine if germline vulnerabilities in mediators of DNA repair pathways can be exploited therapeutically. Overall, it is the right time to fully understand the therapeutic extent of germline vulnerabilities in DNA repair and assess their clinical benefit in cancer patients.

CRediT authorship contribution statement

S.M.S. and E.V.D. contributed equally and substantially to conceptualization, writing - original draft, writing - review & editing, and visualization. R.W.L., M.J.H., M.B.D. and J.E.M. contributed to writing - original draft, and writing - review & editing. S.A. and M.J.E. contributed equally to conceptualization, writing - original draft and writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [M.J.E. has served on scientific advisory board for Biomarker strategies, as an advisor for Windmil Therapeutics, Sanofi/Regeneron, and Syndax; data safety monitoring boards for Astra Zeneca, Seattle Genetics, Takeda, GSK and has received clinical research funding (to the institution) from Apexigen, BMS, Nektar, Precision Oncology, Windmil and Merck. M.J.H. performs collaborative research (with no funding) with the following: Myriad Genetics, Invitae Corporation, Ambry Genetics, Foundation Medicine, Inc. He also performs collaborative research (with no funding) and is part of a Precision Oncology Alliance funded by Caris Life Sciences (cover travel and meals at meetings). S.A. performs collaborative research (with no funding) with Caris Life Sciences, Foundation Medicine, Inc., Ambry Genetics and Invitae Corporation. J.E.M. performs collaborative research (with no funding) with Foundation Medicine, Inc. and Caris Life Sciences. S.A.'s spouse is employed by Akoya Biosciences and has stocks in Akoya Biosciences, HTG Molecular Diagnostics, Abcam Plc., and Senzo Health. S. A., M.J.H., R.W.L., J.E.M. have patents and/or pending patents related to cancer diagnostics/treatment. M.J.E. has pending patent for radiopharmaceuticals to treat small-cell lung cancer. All other authors declare no competing interests.

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Appendix A. Supplementary material

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