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# DNA Repair and Chemotherapy

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## 1. Introduction

Cancer chemotherapy is designed to kill cancer cells, with most agents inducing DNA damage. Highly conserved DNA repair machinery that process DNA damage and maintain genomic integrity developed during the evolution of mammalian cells. Interestingly, in established tumors, DNA repair activity is required to counteract oxidative DNA damage that is prevalent within the tumor microenvironment. If the damaged DNA is successfully repaired, the cell will survive.

In order to specifically and effectively kill cancer cells using chemotherapy that induce DNA damage, it is important to take advantage of specific abnormalities in the DNA damage response machinery that are present in cancer cells but not in normal cells. Such properties of cancer cells may be targets for sensitization and lead to the development of biomarkers. Furthermore, inhibition of a DNA damage response pathway may enhance the therapeutic effects of DNA-damaging agents when employed in combination with these agents.

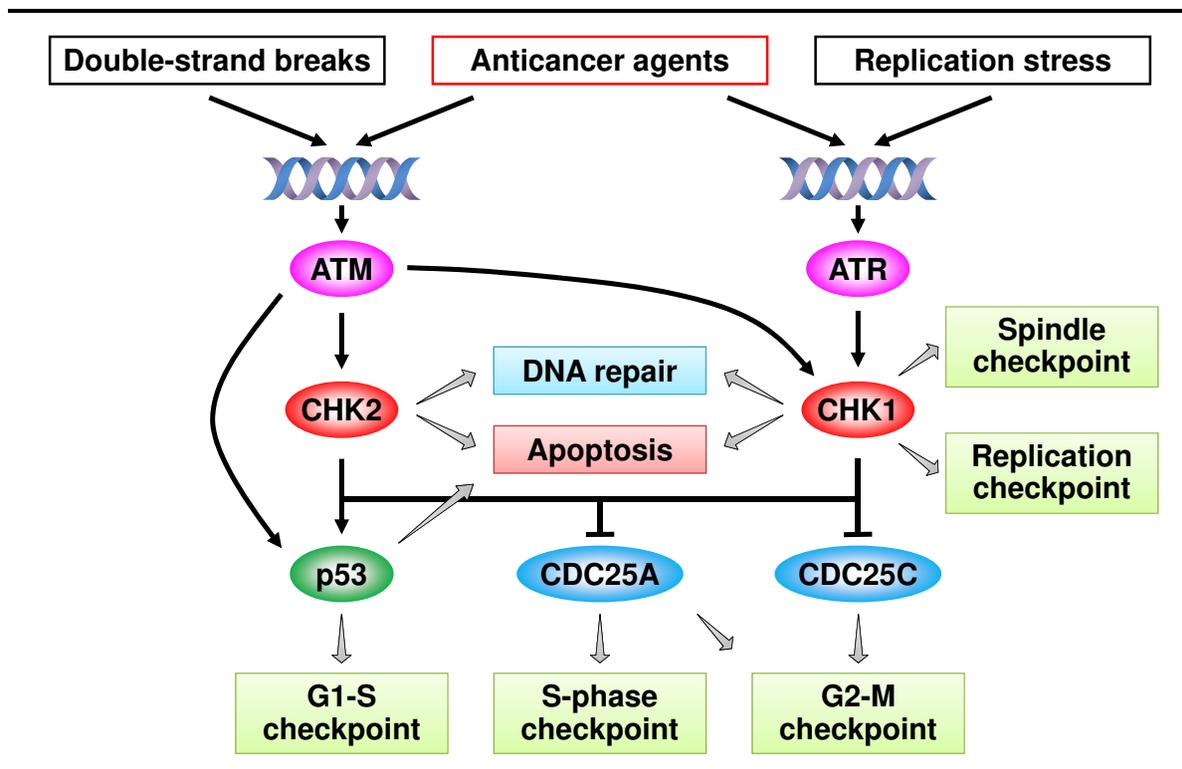
Recently, DNA repair inhibition has emerged as a promising strategy for personalized cancer therapy. Synthetic lethality exploits inter-gene relationships where the loss of function of either one of two related genes is nonlethal, but loss of both causes cell death. Emerging clinical data provide compelling evidence that overexpression of DNA repair factors may have prognostic and predictive significance in patients.

In this chapter, we will provide an overview of major DNA repair pathways and describe recent advances in anticancer therapy with a focus on DNA repair in cancer.

## 2. DNA damage response

The cellular DNA damage response (DDR) involves activation of cell cycle checkpoints to induce cell cycle arrest while repair mechanisms, transcriptional modulation, and/or apoptotic

pathways are activated. DNA damage induced by anticancer agents triggers recruitment of multiprotein complexes and activates a number of pathways, including ataxia telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) signaling pathways. Cell cycle checkpoint kinases (Chk) of Chk1 and Chk2 are functionally redundant protein kinases that respond to checkpoint signals, initiate ATM and ATR, and play a critical role in determining cellular responses to DNA damage [1, 2]. Chk1 is mainly activated through ATR-mediated phosphorylation. Activated Chk1 phosphorylates Cdc25A, which leads to ubiquitin- and proteasome-dependent protein degradation, and downstream to increased phosphorylation of cyclin-dependent kinase (CDK) 2. In contrast, Chk2 is activated mainly by ATM, and activated Chk2 phosphorylates Cdc25A. Activated Chk1 and Chk2 then phosphorylate diverse downstream effectors, which in turn are involved in cell cycle checkpoints (i.e., G1/S-phase, intra-S-phase, and G2/M-phase checkpoints), the DNA replication checkpoint, and the mitotic spindle checkpoint, as well as DNA repair and apoptosis.



ATM, ataxia telangiectasia-mutated; ATR, ATM and Rad3-related; CHK, checkpoint kinase.

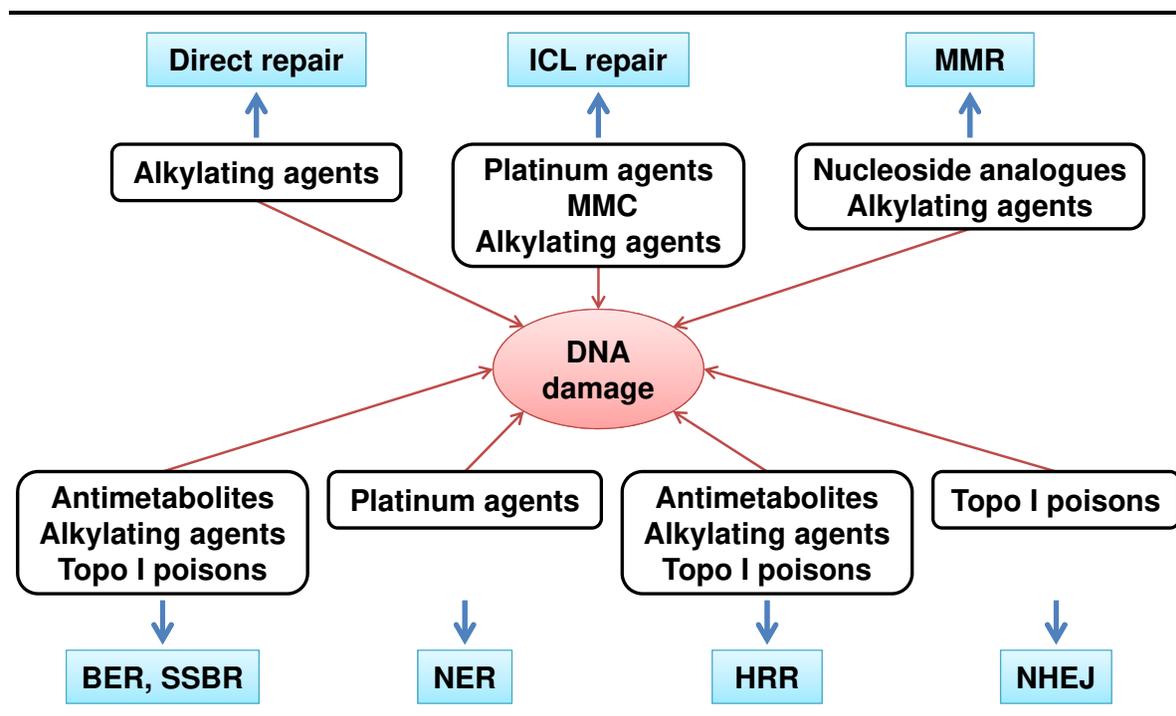
**Figure 1.** DNA-damage response signaling pathways

Consequently, through regulating the activity of CDKs, the progression from one cell cycle phase to another is delayed. The resulting cell cycle arrest allows time for repair, thereby preventing genome duplication or cell division in the presence of damaged DNA.

### 3. DNA repair pathways

DNA repair pathways in mammalian cells maintain genomic integrity. Depending on the type of DNA damage, cells invoke specific DNA repair pathways in order to restore genetic information.

Minor changes to DNA such as oxidized or alkylated bases, small base adducts and single-strand breaks (SSBs) are restored by the base excision repair (BER) pathway [3]. Poly(adenosine diphosphate ribose) (PAR) polymerase (PARP) is important in this process. Upon detection of SSBs, PARP covalently transfers PAR chains to itself and to acceptor proteins in the vicinity of the lesion, thereby facilitating the repair of SSBs. More complex, DNA helix-distorting base lesions, such as those induced by UV light, are repaired by nucleotide excision repair (NER) [4]. Another kind of damage disturbing the helical structure of DNA is represented by base mismatches. Mismatch repair factors recognize and process misincorporated nucleotides as well as insertion or deletion loops that arise during recombination or from errors of DNA polymerases [5].



BER, base excision repair; HRR, homologous recombination repair; ICL, inter-strand crosslink; MMR, mismatch repair; MMC, mytomycin C; NER, nucleotide excision repair; NHEJ, non-homologous end joining; SSBR, single-strand break repair; Topo, topoisomerase.

**Figure 2.** DNA repair pathways and chemotherapeutic agents

Covalent links between the two strands of the double helix represent a type of DNA damage referred to as interstrand crosslinks (ICLs). ICLs represent the most deleterious lesions produced by chemotherapeutic agents such as mitomycin C (MMC), cisplatin and cyclophos-

phamide. ICL repair is complex and involves the collaboration of several repair pathways, namely Fanconi anaemia, NER, translesion synthesis (TLS) and homologous recombination (HR) [6].

So far, four mechanistically distinct DNA double-strand break (DSB) repair mechanisms in mammalian cells have been described: non-homologous end joining (NHEJ), alternative NHEJ, single-strand annealing and HR [7]. NHEJ and HR represent the two major DSB repair pathways, with NHEJ operating throughout the cell cycle and HR being the most active during S-phase [8].

#### 4. Cancer therapies targeting DNA repair mechanism

Alterations in expression of DNA repair may influence cancer biology and aggressive phenotypes. Clinical evidence supports the hypothesis that overexpression of DNA repair factors may have prognostic and predictive significance in patients [9]. Furthermore, highly proliferative cancer cells are hypersensitive to DNA damage because the S-phase is the most vulnerable period of the cell cycle. Therefore, DDR pathways make an ideal target for therapeutic intervention.

Dysfunction of one DNA repair pathway may be compensated by the function of another compensatory DDR pathway, which may be increased and contribute to resistance to DNA-damaging chemotherapy. So, inhibition of the pathway in combination with DNA damage agents will selectively kill cancer cells. These hypotheses are currently being tested in the laboratory and are being translated into clinical studies.

#### 5. Direct repair

The simplest form of DNA repair is direct reversal of the lesion. Direct reversal of the oxidative lesion O6-methylguanine is carried out by the suicide enzyme methylguanine methyltransferase (MGMT) via an active site Cys145 that acts as a methyl recipient, followed by rapid ubiquitin-induced degradation. MGMT expression is one of several factors governing the response to alkylating chemotherapy agents [10, 11].

MGMT demethylates O6-methylguanine lesions, which are formed as a result of erroneous methylation by S-adenosylmethionine (SAM) and other alkylations at the O6 position of guanine that are induced by dietary nitrosamines or chemotherapy agents such as temozolomide (TMZ), dacarbazine (DTIC) and nitrosoureas [12, 13]. The higher levels of MGMT that are frequently observed in tumor tissue compared with normal tissue suggest that its depletion with pseudo-substrates that resemble O6-methylguanine might be a viable strategy to sensitize tumor cells to O6 alkylating agents. However, these pseudo-substrates have shown only marginal clinical benefit [14, 15].

A more promising approach may be the exploitation of reduced MGMT activity owing to epigenetic silencing in some cancers [16]. MGMT promoter methylation correlated with

sensitivity to BCNU in patients with astrocytomas and also correlated with sensitivity to TMZ plus radiotherapy in patients with gliomas [17]. Therefore, MGMT promoter methylation could be useful for stratifying patients for TMZ treatment.

## 6. Base excision repair

BER is responsible for detection and repair of damage caused by a number of mechanisms including alkylation, oxidation by reactive oxygen species (ROS), SSBs and base deamination. BER repairs DNA damage that is therapeutically induced by ionizing radiation, DNA-methylating agents, topoisomerase I poisons such as camptothecin, irinotecan and topotecan [18]. Single-strand break repair (SSBR) and BER are often assumed to be synonymous because they involve the same components and are similar after the initial recognition step. The main components of the pathway are glycosylases, endonucleases, DNA polymerases and DNA ligases, with PARP1 and PARP2 facilitating the process. Damaged bases are first removed by BER glycosylases to form apurinic or apyrimidinic (AP) sites. BER endonucleases then generate an SSB, which along with directly induced SSBs and those generated by topoisomerase (topo) I poisons [19, 20], are the substrates for SSBR. On detecting SSBs, PARP1 rapidly becomes bound and poly(ADP-ribosyl)ated, protecting the nick ends from undesirable recombination and allowing the recruitment of the molecular scaffold protein X-ray repair cross-complementing protein (XRCC) 1 for ongoing repair [21].

The BER pathway is an attractive target for the modulation of chemosensitivity. Early inhibitors of DNA polymerase- $\beta$  (Pol  $\beta$ ), flap endonuclease 1 (FEN1), ligase 1 and ligase 3 enhance sensitivity to ionizing radiation and TMZ. However, the most advanced drugs that target this pathway are AP endonuclease 1 (APE1) inhibitors and PARP-inhibitors (PARP-i, described later). Both APE1 and PARP expression and/or activity are generally higher in tumors [9, 22, 23].

There are two classes of APE1 inhibitor: methoxyamine, which binds the AP site in DNA, and inhibitors of APE1 endonuclease activity. Preclinically, methoxyamine potentiates the cytotoxicity of TMZ [24] and pemetrexed. In a phase I trial of methoxyamine, responses were seen in combination with pemetrexed, and there is an ongoing study with TMZ. Lucanthone, a topo II inhibitor, also inhibits APE1 endonuclease activity and potentiates the cytotoxicity of DNA-methylating agents in breast cancer cells [25]. Novel, more specific, APE1 endonuclease inhibitors increased the persistence of AP sites *in vitro* and increased the cytotoxicity of alkylating agents [26]. The synthetic lethality relationship between HR and APE1 was confirmed by the observed cytotoxicity following ATM inhibitor exposure in APE1<sup>-/-</sup> cells [27].

## 7. Nucleotide excision repair

NER recognizes and repairs base lesions associated with distortion of the DNA helical structure, including UV-induced photoproducts not eliminated by direct repair, and an array

of bulky adducts induced by various exogenous chemical agents. NER removes helix-distorting adducts on DNA and contributes to the repair of intrastrand and ICLs; the xeroderma pigmentosum (XP) proteins and excision repair cross-complementation group 1 (ERCC1) also have crucial roles in both the NER and ICL repair pathways [28]. Deficiency in NER confers sensitivity to platinum agent therapy, which reflects a reduced capacity to repair ICLs [29, 30]. There are currently no small molecule inhibitors of NER, although cyclosporine and cetuximab might down-regulate XPG and ERCC1–XPF expression, respectively. Recent evidence suggests that the efficacy of PARP-i–topo I poison combinations may be most effective in tumors that lack ERCC1–XPF, which are involved in the NER pathway [31].

## 8. Mismatch repair

Mismatch repair (MMR) recognizes and repairs errors introduced during replication. MMR also recognizes and repairs insertion/deletion loops (IDLs), particularly within microsatellite DNA. Hence, “microsatellite instability” (MSI) is recognized as a hallmark of MMR failure [32, 33]. If MSI manifests within tumor suppressor genes, it can produce frameshift mutations that contribute to carcinogenesis in colorectal, endometrial, ovarian, and gastric cancers [34]. Defective MMR increases mutation rates up to 1,000-fold, results in MSI, and is associated with cancer development [35].

Several DDR genes have microsatellites and could be mutated in MSI-high cancer, potentially conferring sensitivity to some DNA-damaging agents [36, 37]. However, defects in MMR cause tolerance to TMZ, platinum agents and some nucleoside analogues, which leads to drug resistance [38, 39]. Some researchers have focused on attempts to reactivate epigenetically silenced MLH1. However, after promising preclinical data that demonstrated chemosensitization [40], clinical trials have shown adverse reactions.

## 9. Homologous Recombination Repair

HR repair (HRR) is crucial for the maintenance of genomic stability, and is the predominant mechanism for DSB. HRR pathway for DSB repair is a highly complex process that involves multiple proteins, and occurs during the S and G2 phases of the cell cycle [41]. Many tumor suppressors participate in this pathway, including BRCA1, BRCA2 and ATM. As heterozygosity at a BRCA allele is associated with effective HR, DSB accumulation induced by PARP-inhibition specifically occurs only in tumor cells with acquired BRCA<sup>-/-</sup> homozygosity [42, 43]. Reasons for “BRCAness” are inactivation of BRCA1 or BRCA2 function caused by aberrant epigenetic or posttranslational modifications, and a wider range of mutations in other genes resulting in defective DSB signaling and HRR. Tumors with HRR defects are highly sensitive to crosslinking agents such as cisplatin, carboplatin and nitrosoureas, and DSBs that are induced by ionizing radiation and topo I poisons.

The high frequency of HRR defects in tumors may underlie the efficacy of cytotoxic therapy and provide a rationale for the use of inhibitors of HRR in the sensitization of tumors with

functional HRR to conventional chemotherapy. Recent evidence suggests that PARP-i induces single agent cytotoxicity in cells with reduced expression of ATM, the checkpoint activator that is activated by DSBs [27, 44]. There are few HRR inhibitors, but mirin is an inhibitor of MRE11 endonuclease activity and thus inhibits HRR function [45]. Germline mutations in the HR protein RAD51D confer susceptibility to ovarian cancer and may be a target for PARP-i in a small subset of women [46]. Other prototype RAD51 inhibitors have been identified but the most common way to target HRR is by inhibition of the ATM–Chk2 or ATR–Chk1 pathways. Hyperactive growth factor signaling and oncogene-induced replicative stress increase DNA breakage that activates the ATR–Chk1 pathway, and some examples of synthetic lethality of checkpoint or DNA repair inhibitors in cells harbouring activated oncogenes have been shown. ATR knockdown was synthetically lethal in cells that were transformed with mutant KRAS [47], and inhibition of Chk1 and Chk2 significantly delayed disease progression of transplanted MYC-overexpressing lymphoma cells in vivo [48].

## 10. Non-homologous end joining

NHEJ is thought to be the major pathway for DSB repair. Damage recognition in NHEJ is performed by the Ku70/Ku80 heterodimer, which binds to the DSB ends with high affinity, possibly tethering the broken ends together. Ku binding recruits and activates the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), forming the DNA-PK complex that phosphorylates other repair proteins including XRCC4-like factor (XLF), Werner syndrome helicase, DNA ligase IV and XRCC4.

DNA-PKcs is a member of the PI3K-related protein kinase family of enzymes that also includes ATM, ATR and mammalian target of rapamycin (mTOR). PI3K inhibitors, such as wortmannin and LY294002, also inhibit DNA-PKcs, and in proof-of-concept studies, these drugs hindered DSB rejoining and enhanced the cytotoxicity of DSB-inducing agents [49, 50]. More potent and specific DNA-PKcs inhibitors have been developed [51, 52] that substantially slow DSB repair and increase the cytotoxicity and antitumor activity of IR, radiomimetics and topo II poisons in cells and xenografts [53, 54]. However, none of these agents have reached the clinical testing stage.

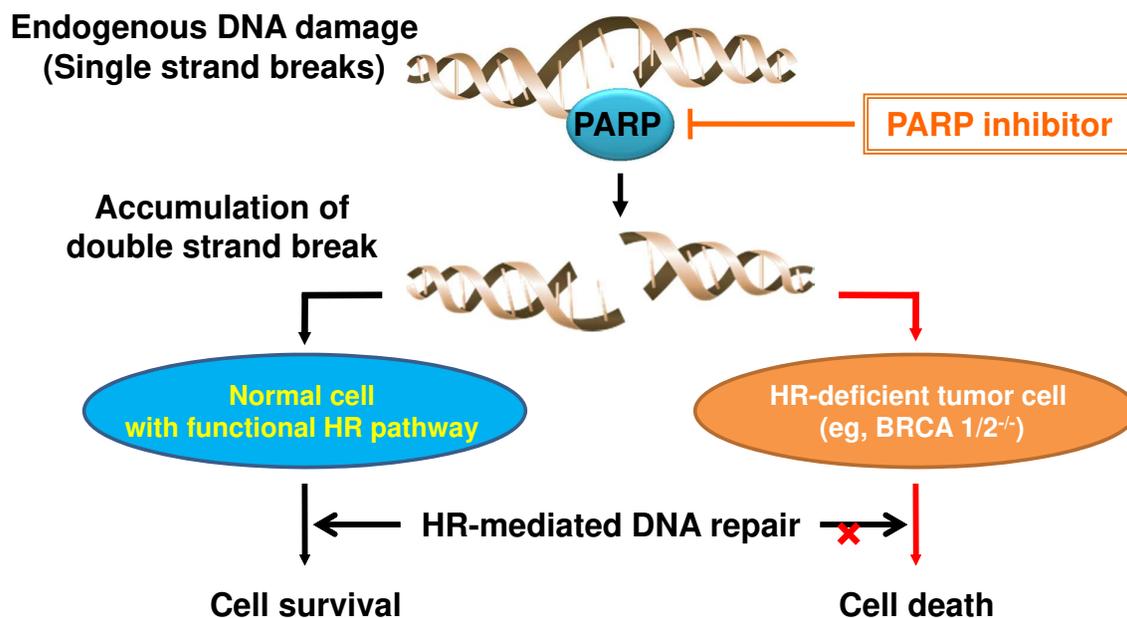
## 11. Translesion synthesis

If damaged DNA bases or adducts are not repaired, they may stall replication forks, which could contribute to genomic instability [55]. Several DNA polymerases can synthesize DNA past DNA lesions. Such TLS contributes to survival. However, errors can occur because these polymerases have no proofreading function and therefore, TLS should be considered a DNA damage tolerance mechanism rather than a DNA repair mechanism. Defects in TLS polymerases contribute to carcinogenesis but also confer sensitivity to DNA-damaging agents, and inhibitors of these polymerases are starting to emerge [56, 57].

## 12. Synthetic lethal strategies

Perhaps the most promising prospect for cancer treatment is the exploitation of dysregulated DDR by the synthetic lethality approach. Synthetic lethality exploits inter-gene relationships where the loss of function of either one of two related genes is nonlethal, but loss of both causes cell death. Loss of some elements of one DNA repair pathway may be compensated by the increased activity of other elements or pathways. The discovery of the synthetic lethality relationship between PARP1 and BRCA suggests that other tumor-specific defects in DSB repair factors may be therapeutically targeted by PARP inhibition.

The best characterized synthetic lethality relationship is between BRCA mutation and PARP1 inhibition [58-60]. BRCA1 and-2 have long been known as tumor suppressors, and their inherited mutation increases susceptibility to breast and ovarian tumors [61]. Both BRCA gene products have a role in the HRR pathway [62]. In BRCA-deficient cells, loss of effective HR leads to DSB persistence and cell death. However, resistance to PARP-i can develop owing to secondary mutations in BRCA1 or BRCA2 that restore their function [63, 64]. In addition, even in BRCA-mutant cells, HRR function and PARP-i resistance can be restored if 53BP1 or DNA-PKcs are also inactivated [65, 66].



HR, homologous recombination; PARP, poly-adenosine-diphosphate-ribose (PAR) polymerase.

**Figure 3.** Tumor selective synthetic lethality

Beyond BRCA1 and BRCA2, their joint interaction partner PALB2 is emerging as a breast cancer susceptibility gene, thus providing another opportunity for PARP-i-based therapies [67]. NVP-BEZ235, a recognized dual PI3K/mTOR inhibitor, was also reported to efficiently

block ATM, ATR and DNA-PK activity. Furthermore, NVP-BEZ235 was found to act as a radio- and chemosensitizer in various cancer cell lines [68, 69] and is currently being tested as a single agent in various phase I/II clinical trials [70, 71].

Synthetic lethality of components of the cell cycle checkpoint machinery could be exploited in cancers harbouring activated oncogenes, since oncogene-induced replication stress activates the ATR-Chk1 signaling pathway. Importantly, more than 50% of human tumors are defective in p53 tumor suppressor function and cell cycle checkpoint inhibitors have been demonstrated to sensitize p53-deficient cancer cells to various anticancer agents in clinical use [72]. The two transducer kinases Chk1 and Chk2 are downstream of ATM and ATR, and several inhibitors of transducer kinases have emerged in recent years. Recently, three novel Chk1 inhibitors, GDC-0425, SCH900776 and LY-2606368, have entered phase I clinical trials either as single agents or in combination with gemcitabine, a nucleoside analogue [73]. Another promising drug that interferes with checkpoint activation is the WEE1 tyrosine kinase inhibitor MK-1775 [74]. MK-1775 is already under investigation in a phase II trial combined with carboplatin in order to assess the benefit for patients with p53-mutated epithelial ovarian cancer. Several agents targeting CDC25 phosphatases that represent key molecules in checkpoint regulation have also been developed [75, 76].

SSBR factors other than PARP1 are potential synthetic lethality partners in DSB repair loss, which is supported by the observed cytotoxicity induced by inhibitors of ATM or DNA-PKcs following knockdown of the BER protein XRCC1 [77]. Recent evidence suggests that relationships between BER and non-HR DNA repair pathways may have potential synthetic lethality. The ATR inhibitor NU6027 was also more profoundly cytotoxic to BER-defective cells and in BER-functional cells treated with a PARP-i, reflecting the complementarity of HRR and BER [78].

Phosphatase and tensin homolog (PTEN) is a negative regulator of the anti-apoptotic PI3K/Akt/mTOR pathway. PTEN has recently been implicated in the maintenance of genomic integrity [79-83]. In the nucleus, PTEN promotes chromosome stability and DNA repair. PTEN loss-of-function could be an effective target for treatment strategies. Since PTEN deficiency causes a defect in HR, cells rely on PARP for the repair of DSBs. PTEN deficiency therefore sensitizes cancer cells to PARP inhibition [84-86]. Mendes-Pereira et al. [84] tested for synthetic lethality in HCT116 colorectal tumor cells transfected with a PTEN-mutant cDNA clone. Homozygosity for PTEN mutation was associated with a 20-fold increase in sensitivity to PARP-i in vitro and in vivo. Ectopic expression of RAD51 in a PTEN-deficient cell line overcame PARP-i sensitivity, supporting the proposed link between PTEN mutation and reduced RAD51 expression. Similar results were demonstrated in uterine endometrial carcinoma [85]. In primary PTEN<sup>-/-</sup> mouse astrocytes, reduced transcription of the RAD51 paralogs was associated with sensitivity to PARP inhibition [86], while PTEN disruption in colorectal cancer cells resulted in reduced MRE11 accumulation at DSBs that is also associated with PARP-i sensitivity [87]. Prostate cancers exhibiting PTEN loss often harbor a genetic rearrangement leading to TMPRSS2-ERG fusion. The TMPRSS2-ERG protein product promotes the formation of DNA DSBs and interacts with PARP, thus sensitizing cells to PARP inhibition [88, 89]. In lung cancer cells, PTEN deficiency potentiated the synergistic effect of

olaparib and cisplatin combination treatment [90], while rucaparib sensitized PTEN-deficient prostate cancer cells to ionizing radiation [91]. In melanoma cells, PTEN loss may contribute to BRAF and APE1 inhibition [92, 93]. Retrospective analysis of genetic alterations and PTEN status in tumors taken from patients who are participating in an ongoing clinical trial will provide information for the development of synthetic lethal treatment involving PTEN [94].

Mutations of the von Hippel–Lindau (VHL) tumor suppressor gene occur in the majority of sporadic renal cell carcinomas (RCC). The lack of VHL function in cells results in decreased repair capacity [95]. For example, the suppressor of cytokine signaling 1 (SOCS1) promotes nuclear redistribution and K63 ubiquitylation of VHL in response to DSBs. Loss of VHL function or VHL mutation that compromises K63 ubiquitylation attenuates the DDR, resulting in decreased HRR and persistence of DSBs [96]. Furthermore, loss of VHL function is associated with stabilization of hypoxia-inducible factor  $\alpha$  (HIF $\alpha$ ). The exposure of cells to hypoxia markedly enhances genetic instability caused by exogenous genotoxins, and HIF activation decreased NER [97]. Recently, synthetic lethal (SL) partner of VHL was identified from a screening of large volumes of cancer genomic data using a small interfering RNA screen. The VHL-deficient cells are significantly more sensitive to the knockdown of the predicted VHL-SL partners [98]. DNA repair pathway abnormalities involving VHL dysfunction might be therapeutic targets.

Many strategies based on the concept of synthetic lethality have so far only been investigated in preclinical settings.

### 13. PARP inhibitor

A number of potential PARP-i have been identified. In xenograft and in vitro models, PARP-i have been demonstrated to potentiate the action of a wide variety of damaging agents including platinum, the alkylating agents TMZ and cyclophosphamide, the nucleoside analogue gemcitabine, the topo inhibitor irinotecan, and ionizing radiation [90]. Furthermore, preclinical studies also suggested the potential use of PARP-i in sporadic cancers that share phenotypical features with cancers arising from hereditary BRCA mutations, a phenomenon that is referred to as “BRCAness” [91]. Many additional phase I and II trials are currently underway, examining the combination with a variety of agents including carboplatin, 5-fluorouracil and oxaliplatin, cisplatin and paclitaxel, topotecan, gemcitabine, and radiotherapy [92]. For example, rucaparib has been evaluated in phase I and II studies in combination with TMZ for malignant melanoma, demonstrating successful PARP inhibition at the tissue level and probable anticancer activity, but significant myelosuppression caused dose-limiting toxicity [93].

An initial phase I study of olaparib in a cohort enriched for BRCA1/2 mutation carriers demonstrated evidence of in vivo anti-PARP activity and evidence of response in 40% of BRCA carriers [60]. Phase II trials of olaparib for breast or ovarian cancer associated with BRCA1/2 mutations were favorable, suggesting antitumor efficacy [94, 95]. Good responses were also seen in patients with BRCA-associated breast and ovarian cancers, and even in unselected

patients with high-grade serous ovarian cancer [96, 97]. However, olaparib did not progress to a phase III trial for hereditary BRCA mutation-associated breast cancer due to economic concerns [98].

Iniparib has been evaluated in a phase II study of metastatic triple-negative breast cancer treatment in combination with gemcitabine and carboplatin. A significantly improved median overall survival was demonstrated compared with gemcitabine and carboplatin, without increased toxicity. However, a phase III trial failed to meet co-primary endpoints of overall and progression-free survival improvement, and after further disappointing results in a phase III non-small cell lung cancer trial, iniparib has been suspended from further development [99].

A good safety profile was also observed with veliparib in combination with TMZ. This was associated with early positive results in metastatic colorectal and BRCA-deficient breast cancers, although the combination was associated with poor response and no progression-free or overall survival improvement in advanced melanoma. Likewise, phase II investigation of rucaparib in BRCA1/2-mutated breast or ovarian cancer demonstrated PARP activity inhibition and evidence of a tumor response. The oral PARP1/2 inhibitor niraparib has also been evaluated at phase I and was shown to possess an acceptable safety profile and probable antitumor activity. Other PARP-i including orally bioavailable agents are currently being tested in clinical trials [100].

Clinical trials of PARP-i have generally been disappointing owing to toxicity, which may be due to use of a dose of PARP-i that was established as safe when used as a single agent. In general, preclinical data indicated that the MTD of single agent PARP-i was much higher than MTD of PARP-i when combined with another cytotoxic agent such as TMZ [101, 102]. This is because almost total inhibition of PARP-i is needed to render endogenous DNA damage cytotoxic, but this level of inhibition is not necessary to render the additional burden of deliberately introduced DNA damage cytotoxic, both in the tumor and in proliferating normal tissues. In addition, secondary BRCA2 mutations have been identified, which restore the full-length protein, thereby re-establishing BRCA2 functions and conferring PARP-i resistance [103]. A major challenge of using PARP-i is the acquired resistance of initially PARP-i-sensitive cancer cells due, for example, to the loss of p53-binding protein-1 (53BP1) or to overexpression of multidrug-resistance efflux transporters [104, 105]. The data described above suggest that the clinical utility of PARP-i in combination with chemotherapy may be limited in tumors in view of its narrow therapeutic index.

## 14. Predictive biomarkers

Relevant biomarker assays should predict the functionality of DNA repair pathways, rather than just providing information about mutations or expression levels of proteins involved in the DNA repair pathway. Furthermore, such detailed molecular profiling of cancer versus normal tissue from a given patient is critical to maximize the potential of personalized cancer drugs in terms of both therapeutic success and cost-effectiveness.

A general marker of DNA damage is the phosphorylation of histone H2AX by ATM, ATR and DNA-PK.  $\gamma$ H2AX foci, formed at sites of DSBs, or increased levels of  $\gamma$ H2AX, may be measured by immunofluorescence microscopy, flow cytometry or immunoblotting and used to detect DNA damage [106]. The increase and/or persistence of  $\gamma$ H2AX can be used to demonstrate the inhibition of PARP, DNA-PK, ATR and Chk1. To directly measure the effect of a molecularly targeted agent, immunological methods may be used to detect the product. For example, activation of DNA-PK and ATM in response to DNA damage can be determined by measuring their autophosphorylation with phospho-specific antibodies, and PARP activity may be measured by immunodetection of the ADP-ribose polymer product, to guide PARP-i clinical trials [60, 107-109]. In multiple clinical trials, PARP activity in peripheral mononuclear blood cells has been used as a marker of effective inhibition [110, 111].

An alternative approach is to assess HRR function in fresh viable tumor material by measuring the number of RAD51 foci following *ex vivo* DNA damage induction [112-114]. In the ovarian cancer study, this was further analyzed in BRCA2-mutated pancreatic cancer cell clones to predict RAD51 foci formation as a marker of HR, and to examine for sensitivity to PARP inhibition.

When inactivation of a single gene has been identified as a crucial determinant of sensitivity, it may then be used to select patients for the appropriate therapy. For example, low levels of the NER endonuclease ERCC1 correlate with cisplatin sensitivity in several cancers [30, 115, 116]. Several studies report methods to identify tumors with non-germline HRR defects: gene expression profiling, methylation-specific arrays, immunohistochemistry analysis of tissue microarrays and copy number aberrations by array comparative genomic hybridization. [117-121]

Immunohistochemistry analysis of formalin-fixed, paraffin-embedded samples may be a useful tool for identifying DDR defects in order to stratify patients. To measure the effect of an agent that directly causes DNA DSBs in all phases of the cell cycle, patient-derived lymphocytes can be used [122]. Owing to the invasive procedures that are needed to obtain tumor material, except in the case of hematological malignancies, circulating tumor cells offer the best hope of routinely obtaining suitable material [123].

## 15. Conclusion

DNA repair mechanisms play an essential role in promoting genomic stability. On the other hand, impaired DNA repair capacity in cancer cells may result in a favorable response to chemotherapy. Many conventional therapeutic regimens that effectively kill cancer cells are based on DNA damage. However, most chemotherapeutic regimens cause severe side effects that limit their therapeutic potential. Inhibition of DNA repair is a new paradigm in cancer therapy, and there is heightened interest in the therapeutic potential of these inhibitors that selectively target tumors with minimal host toxicity.

The synthetic lethal approaches targeting the individual genetic profile of the tumors are under clinical development. The molecular characterization of tumors and reliable biomarkers are

needed for effective personalized therapy. Further research is necessary in order to determine the most appropriate treatment for patients.

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