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Overview

DNA Repair: Translation to the Clinic☆

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Abstract

It has been well established that an accumulation of mutations in DNA, whether caused by external sources (e.g. ultraviolet light, radioactivity) or internal sources (e.g. metabolic by-products, such as reactive oxygen species), has the potential to cause a cell to undergo carcinogenesis and increase the risk for the development of cancer. Therefore, it is critically important for a cell to have the capacity to properly respond to and repair DNA damage as it occurs. The DNA damage response (DDR) describes a collection of DNA repair pathways that aid in the protection of genomic integrity by detecting myriad types of DNA damage and initiating the correct DNA repair pathway. In many instances, a deficiency in the DDR, whether inherited or spontaneously assumed, can increase the risk of carcinogenesis and ultimately tumorigenesis through the accumulation of mutations that fail to be properly repaired. Interestingly, although disruption of the DDR can lead to the initial genomic instability that can ultimately cause carcinogenesis, the DDR has also proven to be an invaluable target for anticancer drugs and therapies. Making matters more complicated, the DDR is also involved in the resistance to first-line cancer therapy. In this review, we will consider therapies already in use in the clinic and ongoing research into other avenues of treatment that target DNA repair pathways in cancer.

Key words: DNA damage response; DNA repair; radiation; radiobiology

Conundrum: a Double-edged Sword of DNA Repair Perturbation

It is generally believed that the progression of a cell from a normal to a tumorigenic state occurs through a series of gene-altering steps that ultimately evade genomic stability-maintaining mechanisms and instead lead to genomic instability. Indeed, genomic instability is one of the hallmarks of cancer, reflecting the path from which the cancerous cells arose [1]. In normal cells, genomic integrity is protected by the DNA damage response (DDR), which describes the collection of pathways capable of detecting and repairing different types of DNA damage. Deficiencies in the DDR and its repair pathways, whether acquired or inherited, can accelerate the accumulation of mutations and help augment the loss of stability that ultimately gives rise to malignancy. Paradoxically, however, although deficiencies in DNA repair pathways can first lead to a loss of genomic integrity through the accumulation of mutations, the proteins involved have proven to be viable and efficacious targets for cancer therapies, while at the same time also contributing to resistance to first-line cancer treatments. To reconcile these differences, it is important to recognise that cancerous cells arise from normal, non-malignant cells, and thus share many of the same characteristics as their unaffected kin. A major goal in creating more effective cancer therapies is to find differences between cancerous and non-malignant cells that allow treatments to more specifically target the unhealthy cells, therefore minimising the toxicity cancer patients experience while undergoing therapy. An important clinical term regarding this notion of targeted toxicity is the therapeutic index or ratio, which is defined as the amount of tumour control that can be achieved for a given amount of healthy tissue toxicity [2]. The higher the ratio, the better the efficiency of the treatment in targeting cancerous as opposed to non-cancerous cells, minimising side-effects to healthy tissues. One way to increase the therapeutic ratio is to use synthetic lethality. Synthetic lethality is achieved when the

☆ Clinical trials were found through https://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/search. Other information was compiled through a literature search.

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simultaneous deficiency of two or more genes causes cell death, whereas a deficiency in only one is otherwise non-lethal [3]. Cancerous cells generally have higher incidences of DNA repair pathway deficiencies, resulting in a higher dependence on any remaining intact DNA repair pathways to maintain genomic stability [4]. This dependency renders the cancerous cells vulnerable to agents that target the remaining intact pathways in a synthetic lethal way that would otherwise be harmless to normal, healthy cells, and is a rapidly expanding field of research in cancer treatments [5,6]. A closely related concept to synthetic lethality that also offers a promising new strategy for increasing the therapeutic ratio through the targeting of the DDR is 'acquired vulnerability', otherwise known as 'collateral sensitivity'. This term describes the phenomenon in which acquired resistance to one drug confers hypersensitivity towards a different reagent, thereby offering the possibility of clinical exploitation should the vulnerability be identified [7]. Research has already started to find that some of these acquired vulnerabilities are tied to the DDR, further underscoring the notion that the DDR is an invaluable target in the quest to find novel therapeutic approaches in the treatment of cancer [8].

Types of DNA Repair

The cell has a complex system of interconnected DNA repair pathways that allows it to respond to a variety of different types of damage and regulate the outcomes of the intended repair (Figure 1). Single-strand DNA (ssDNA) damage can include a wide variety of insults, such as single-strand breaks (SSBs), deamination of bases, errors in base matching incurred during DNA replication and the creation of bulky adducts. There are, in the broadest of terms, three main pathways that are responsible for the repair of ssDNA damage: base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR) [9]. BER removes damaged bases that do not significantly alter the overall structure of DNA, as opposed to NER, which can recognise and repair the bulky, structurally altering ssDNA lesions [10]. Finally, MMR functions as a method of proofreading after DNA replication to catch any mismatched base pairs that were overlooked during DNA synthesis by DNA polymerases [10]. Mutations that impair any of these pathways can lead to disorders that substantially increase the lifetime risk of developing cancer, such as MUTYH-associated polyposis (BER), xeroderma pigmentosa (NER) and Lynch syndrome (MMR) [11]. DNA can also be affected by inter-strand crosslinks (ICLs), which form when two base pairs are covalently bound together [12]. ICLs are especially cytotoxic to cells, as the covalent bond can block replication and/or transcription, and when left unrepaired, can lead to mutation and chromosomal breakage [12]. As with ssDNA repair pathways, defects in the DDR pathways responsible for repairing ICLs can lead to diseases that dramatically increase the chances of tumorigenesis: Fanconi anaemia is a rare disease that is caused by mutation of the Fanconi anaemia subtype (FANC) proteins. The FANC proteins function in the Fanconi anaemia pathway, which is essential for the maintenance of genomic integrity through the repair of ICLs [12].

In addition to ssDNA damage, cells can also encounter double-strand breaks (DSBs), the most deleterious type of DNA damage. DSBs are repaired by two main pathways: non-homologous end joining (NHEJ) and homologous recombination repair (HRR) [13]. NHEJ is a form of repair template-independent repair and thus is an error-prone mechanism of repair active from G_1 through G_2. In some cases after a DSB has occurred, the ends of the broken

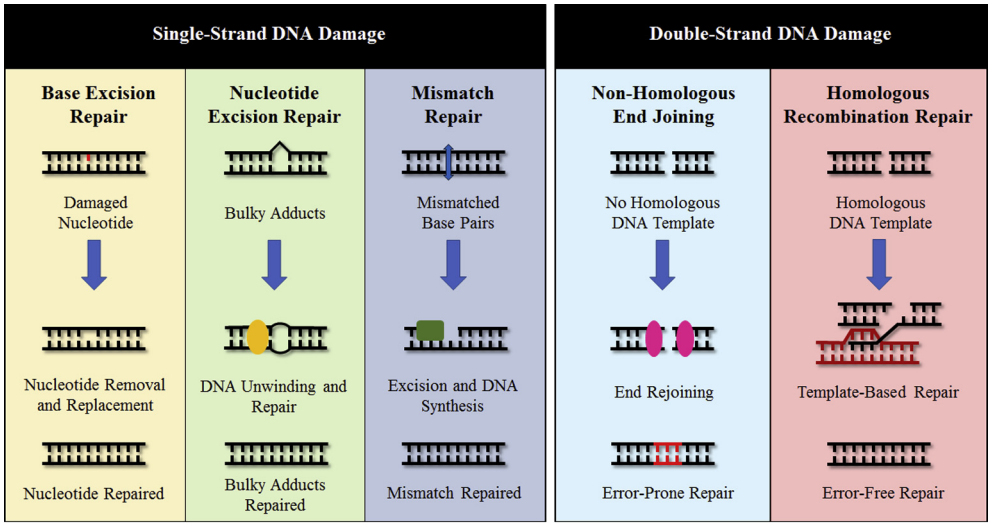

Fig 1. DNA repair pathways of single-strand DNA (ssDNA) damage and DNA double-strand breaks (DSBs). From left to right for ssDNA repair: base excision repair (BER) is used to repair damage to nucleotides that do not significantly alter the DNA structure. Nucleotide excision repair (NER) mends structurally altering DNA damage, such as bulky adducts. Mismatch repair (MMR) fixes pairs of nucleotides that were mismatched during DNA synthesis. Non-homologous end joining (NHEJ) repairs DNA DSBs without the use of a homologous DNA template by rejoining the broken DNA ends together and is prone to introducing errors. Homologous recombination repair (HRR) uses a homologous DNA template to repair DNA DSBs without error.

strands will undergo resection, where degradation of overhangs will occur via exo- or endonuclease activity to stick the two broken DNA ends back together [14]. HRR, on the other hand, is considered to be an error-free method of DSB repair and occurs mainly in the S and G_2 phases of the cell cycle when there is a sister chromatid available for use as a repair template [15]. More extensive end resection is carried out to the broken ends of the DSB as opposed to in NHEJ, where more minimal resection is needed. Of the two pathways, NHEJ is favoured over HRR, even during the S and G_2 phases where HRR is more active, with some studies showing a 4:1 ratio of NHEJ to HRR in mammalian somatic cells [14]. Similar to ssDNA repair pathways, the impairment of NHEJ or HRR through the mutation of regulatory or involved proteins can lead to an increased risk of carcinogenesis and tumorigenesis due to accumulation of unresolved DSBs in the genome. For example, certain mutations in breast cancer 1/2 (BRCA1/2), proteins essential to proper HRR, are linked to an increased risk of developing a wide range of different cancers, including breast, prostate, colon, ovarian and pancreatic, with increased lifetime risks for cancer development as high as 55% [16]. In addition, patients with LIG4 syndrome have a predisposition to developing lymphoid malignancies due to a deleterious mutation in the gene encoding protein DNA Ligase IV, resulting in impaired NHEJ [17].

Poly (ADP-ribose) Polymerase Inhibitors

One of the most developed cancer therapies targeting DNA repair pathways that has risen to prominence within the last few years is the use of poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi). PARPs are a class of 17 nuclear enzymes involved in multiple cellular functions [18]. These proteins, which can transfer either one or multiple (ADP-ribose) units from NAD+ onto substrates to make poly (ADP-ribose) (PAR) chains, are found in all eukaryotes except yeast [19]. PARP1 has been found to play a crucial role in the DDR, including in ssDNA repair, NHEJ and HRR [20–22]. PARP1 is recruited to sites of damage for various types of damage, aided by its DNA-binding domain, and has a number of functions, such as binding SSBs, recruiting downstream DNA repair proteins and promoting HRR at stalled and/or collapsed replication forks [22]. Although PARPi were first found over 30 years ago, only in 2005 was it demonstrated through the work of two independent research groups that the use of PARPi is synthetically lethal in cells deficient in HRR, such as when there are mutations in the BRCA1/2 proteins [21,23]. Indeed, PARPi have had enough success that as of October 2018, four PARPi have been approved by the US Food and Drug Administration (FDA): olaparib (Lynparza), rucaparib (Rubraca), niraparib (Zejula) and the newest one, talazoparib (Talzenna) [24]. These drugs have been approved for use in patients with *BRCA1/2* deficiencies in ovarian cancer and by the European Medical Agency in patients who have responded to platinum-based chemotherapy with relapsed *BRCA1/2* mutant ovarian, fallopian tube or primary peritoneal cancers [25,26]. Olaparib, the first PARPi to be approved by the FDA in 2014, has also been approved for clinical use in patients with *BRCA1/2* mutations and HER2-negative breast cancer [24,26,27]. These drugs have also shown promise in treating other types of HRR-deficient breast and prostate cancer. However, the exact mechanism describing this synthetic lethal relationship has not yet been fully elucidated [28]. Originally, it was hypothesised that the synthetic lethality between PARP inhibition and BRCA1/2 mutation relied on the induction of persistent SSBs after PARPi inhibition. During replication, the replication fork would collapse when encountering the SSBs, and thus potentially create a DSB that was unable to be properly repaired by HRR [29]. In the absence of HRR, other DNA repair processes more prone to introducing deletions, mutations and potentially genomic rearrangements would take over, often leading to cell death [29]. This model has changed with new evidence suggesting some of the PARPi 'trap' PARP1 onto DNA, preventing its release and thus stalling repair [29]. However, as with many other types of cancer treatment, tumour resistance to PARPi is frequently seen and represents a major hurdle in long-term treatments [30]. The mechanism for acquired resistance has been suggested to fall into two broad main categories: secondary mutations restore necessary minimal HRR function, rendering the previously synthetic lethal phenotype ineffective [29]; resistance can occur in an HRR-independent manner, such as through PARP protein expression loss, rendering PARPi ineffective [29,31]. Research is already underway to establish what therapies can be used to prevent and/or counter PARPi resistance, taking advantage of the idea of acquired vulnerability, but more work needs to be done to make this goal a reality [8].

Kinase Inhibitors

Another route of targets that has seen moderate success in the cancer therapeutic field includes the class of DDR kinase inhibitors. As of January 2019, the FDA has approved over 30 kinase inhibitors targeted at the treatment of cancers [32]. Phosphorylation plays a critical role in the regulation of many DDR pathways. Ataxia telangiectasia mutated (ATM), which is a key player in the repair of DSBs through the HRR pathway and a serine/threonine kinase in the phosphatidylinositol 3-kinase (PI3K)-related kinase (PIKK) family, acts as an early signalling protein in the DDR and is responsible for the phosphorylation of hundreds of downstream targets [33,34]. The protein is named after a rare autosomal recessive disorder, ataxia telangiectasia, which results from mutations in the ATM gene. Patients who suffer from this disorder have symptoms such as radiosensitivity, immunodeficiencies and an increased risk of cancer [35]. Studies have shown that ATM is synthetic lethal with PARP deficiencies and that ATM inhibitors can sensitise cells to DSB-inducing reagents and ionizing radiation [36,37]. ATM inhibitors are currently being explored in a clinical setting: for example, the ATM inhibitor AZD0156 in conjunction with olaparib (a PARPi) or irinotecan (a

topoisomerase inhibitor) is currently under review in an early clinical phase I trial (clinical trial NCT02588105) [35]. Ataxia telangiectasia and Rad3-related protein (ATR) shares many of the same characteristics as ATM. Another PIKK family member and serine/threonine kinase, ATR also functions as an early signalling kinase in the DDR response, primarily following replication stress. Preclinical studies have found that ATR has a synthetic lethal relationship with several DDR players, including XRCC1 and ATM, and is currently under clinical investigation for its potential as a target in cancer therapies [38,39]. VX-970, or M6620, a potent ATR inhibitor, is currently involved in phase II trials, used either as a single agent or in tumours with DNA repair deficiencies. A phase I trial in which VX-970 was used alone or in combination with carboplatin showed early evidence of potential efficacy [40]. Checkpoint kinase 1 (CHK1), a major downstream effector of ATR, and WEE1, are additional kinases of interest in the clinical setting. CHK1 is involved in a multitude of different functions in the cell and prevents cells with damaged or incompletely replicated DNA after exposure to ionizing radiation or chemotherapeutic drugs moving from G_2 onto mitosis. CHK1 inhibitors have already been used in National Institutes of Health (NIH) phase I clinical trials of monotherapy, such as LY2606368 (prexasertib) (clinical trial NCT02203513) [41]. WEE1, which is involved in triggering the DDR after DNA damage has occurred, is also under clinical investigation as a target for inhibition in the treatment of certain cancers [42]. AZD1775, a WEE1 inhibitor, is currently being tested in phase I and II trials, both as monotherapy and in combination therapies (e.g. clinical trial NCT02593019 and those listed in Table 1, respectively).

Attempts have also been made to inhibit the protein DNA-dependent protein kinase (DNA-PKcs), another member of the PIKK group that serves a crucial role as a main regulator of the NHEJ pathway. DNA-PK, a complex made of the catalytic subunit DNA-PKcs and the Ku heterodimer, is itself a target of ATM and ATR and is dependent on the binding of DNA for activation [43,44]. Once bound to Ku and DNA, DNA-PKcs helps in the recruitment of other NHEJ proteins to begin DNA resection at the broken ends of the DSBs and later DNA ligating complex proteins to join the DNA ends. Interestingly, it has been found that in cell lines with defective DNA-PK function, whether through a lacking of Ku or DNA-PKcs, there exists a hypersensitivity to ionizing radiation and chemical agents that cause DSBs [44]. On the flip side, upregulation of DNA-PK activity has been correlated with increased resistance to DNA damage in some cancers [44]. Therefore, DNA-PK is a promising target for anticancer therapies. One of the first DNA-PKcs inhibitors, wortmannin, was isolated from the fungi *Penicillium funiculosum* in 1957 [45]. Wortmannin is a non-specific PI3K family inhibitor and has been found to be an effective radiosensitiser [46]. However, wortmannin has proven to have limited clinical application, given that the substance is poorly soluble in aqueous solutions, non-specific and toxic [47]. Subsequently, other general PI3K inhibitors have been developed with the aim of increasing clinical applicability while maintaining its sensitising properties, such as LY294002 and its prodrug SF1126. Although LY294002 did not reach clinical trials due to similar issues as seen in wortmannin, together with a quick metabolic clearance rate of 1 h, SF1126 has so far successfully completed a phase I clinical trial that ended in 2011, which found the drug to be well-tolerated with promising results, and is undergoing a second phase I trial in patients with advanced hepatocellular carcinoma (NCT00907205 and NCT03059147, respectively) [44,48,49]. NU7441, a DNA-PKcs-specific inhibitor, is also being studied and has shown promising preclinical effects on certain types of cancer, such as non-small cell lung cancer [50].

Radiation Therapy: Combinatorial Approach

Radiation therapy, or the use of ionizing radiation in the treatment of cancer, has been used for over a century and functions to exploit the genomic instability phenotype of cancerous cells, as a deficiency in the ability to repair DSBs frequently results in an increased sensitivity to ionizing radiation [51]. Since its inception, radiation therapy has seen significant improvements that reduce toxicity to normal tissue, although this toxicity still remains a limiting factor [4]. One area of improvement that has been of great interest is the induction of 'artificial synthetic lethality,' where radiation therapy is combined with specific targets to DNA repair pathways redundant in non-malignant cells, but crucial for cancerous cell survival. This combination of radiation therapy and inhibition of DNA repair pathways comes with the goal to increase the therapeutic index by conferring increased ionizing radiation sensitivity only to cancerous cells [52]. Current radiotherapy techniques are used such that the dose is targeted to the tumour to spare the surrounding healthy tissue from treatment, which also functions to limit the amount of damage normal tissues would receive after application of a systematic inhibitor of a DNA repair protein [53]. Together, the targeted radiation therapy and inhibited DNA repair in cancer cells would potentially lead to an increase in the therapeutic index, allowing for a reduction in the effective radiation dose while limiting toxic side-effects.

There have been several agents targeting DNA repair pathway proteins that have been found in preclinical studies to be effective radiosensitisers, many of which are under current clinical investigation in phase I and II trials (Table 1). One protein that has been shown in preclinical studies to increase radiosensitivity is Artemis, an endo/exonuclease in the NHEJ pathway that is recruited and activated by DNA-PKcs to process broken DNA ends at DSBs [54]. Patients who have null mutations for *Artemis* show extreme radiosensitivity, making Artemis a target of interest for its projected efficiency in working synergistically with radiation therapy, as well as etoposide treatment (which, similar to ionizing radiation, causes DSBs) [55]. However, to date, no inhibitor of Artemis has been found, although compounds are currently being screened to identify potential inhibitors

Table 1
A list of clinical trials that have taken place or are currently ongoing in the US and Europe that combine radiation therapy with the listed DNA damage response (DDR) inhibitors. The phase of the trials, cancer types being investigated, current status as of submission, names of the drugs and the respective DDR targets, and trial identifier numbers have been listed

Phase	Cancer	Status	Drug	Drug target	Trial identifier
I	Head and neck	Completed	Olaparib	PARP	NCT01758731
I	Triple negative breast cancer	Recruiting	Olaparib	PARP	NCT03109080
II	Inflammatory breast cancer	Recruiting	Olaparib	PARP	NCT03598257
I	Inoperable breast cancer	Recruiting	Olaparib	PARP	NCT02227082
I	Head and neck	Recruiting	Olaparib	PARP	NCT02229656
I/II	Metastatic castration-resistant prostate cancer in bone	Recruiting	Olaparib	PARP	NCT03317392
I	Soft-tissue sarcoma	Recruiting	Olaparib	PARP	NCT02787642
I	Small cell lung cancer	Recruiting	Olaparib	PARP	NCT03532880
I	Head and neck	Recruiting	Olaparib	PARP	NCT02308072
I/II	Unresectable high-grade glioma	Recruiting	Olaparib	PARP	NCT03212742
II	Glioblastoma	Ongoing	Olaparib	PARP	2014-001216-19
I/II	Diffuse pontine glioma	Completed	Veliparib	PARP	NCT01514201
II	Non-small cell lung cancer with brain metastases	Completed	Veliparib	PARP	NCT01657799
I	Peritoneal carcinomatosis, epithelial ovarian, fallopian, and primary peritoneal	Completed	Veliparib	PARP	NCT01264432
I	Brain metastases	Completed	Veliparib	PARP	NCT00649207
I	Rectal cancer	Completed	Veliparib	PARP	NCT01589419
I	Recurrent breast cancer	Completed	Veliparib	PARP	NCT01477489
II	Malignant glioma without H3 K27M or BRAFV600E mutations	Recruiting	Veliparib	PARP	NCT03581292
I	Pancreatic	Active	Veliparib	PARP	NCT01908478
I	Triple negative breast cancer	Recruiting	Rucaparib	PARP	NCT03542175
I	Castrate-resistant prostate cancer	Recruiting	Niraparib	PARP	NCT03076203
I	Non- and small cell lung cancer, and neuroendocrine	Recruiting	VX-970 (M6620)	ATR	NCT02589522
I	Oesophageal and other	Not yet recruiting	VX-970 (M6620)	ATR	NCT03641547
I	HPV-negative head and neck squamous cell carcinoma	Recruiting	VX-970 (M6620)	ATR	NCT02567422
I	Brain cancer	Recruiting	AZD1390	ATM	NCT03423628
I	Advanced solid tumours	Recruiting	M3814	DNA-PK	NCT03724890
I	Advanced solid tumours	Recruiting	MSC2490484A	DNA-PK	NCT02516813
I/II	Rectal cancer	Not yet recruiting	M3814	DNA-PK	NCT03770689
I	Head and neck	Recruiting	LY2606368 (Prexasertib)	CHK1/CHK2	NCT02555644
I	Head and neck	Recruiting	AZD1775 (Adavosertib)	WEE1	NCT03028766
I	Cervical, vaginal, and uterine	Recruiting	AZD1775 (Adavosertib)	WEE1	NCT03345784
I	Intermediate-/high-risk squamous head and neck	Recruiting	AZD1775 (Adavosertib)	WEE1	NCT02585973
I/II	Unresectable adenocarcinoma of the pancreas	Active	AZD1775 (Adavosertib)	WEE1	NCT02037230
I	Diffuse intrinsic pontine glioma	Recruiting	AZD1775 (Adavosertib)	WEE1	NCT01922076
I	Glioblastoma	Recruiting	AZD1775 (Adavosertib)	WEE1	NCT01849146
I	Soft-tissue sarcoma	Recruiting	AMG-232	MDM2	NCT03217266
I/II	Non-small cell lung cancer	Completed	NFV	AKT	2006-001031-22

PARP, poly (ADP-ribose) polymerase; ATR, ataxia telangiectasia and Rad3-related protein; ATM, ataxia-telangiectasia mutated; DNA-PK, DNA protein kinase; CHK, checkpoint kinase. MDM2, Mouse double minute 2 homolog; AKT, Protein kinase B (AKT is more a historical name than something that actually stands for anything).

(NIH 5F31GM116569-03). NU7441, mentioned previously as a DNA-PKcs-specific inhibitor, has also been shown to increase cell death after ionizing radiation and etoposide treatment in different types of colon cancer cells in a DNA-PKcs-dependent manner [56]. However, NU7441 has proven to be clinically unusable due to problems with bioavailability and solubility, and other DNA-PKcs inhibitors are currently being investigated in both preclinical and clinical phases (Table 1) [57]. PARPi, including the four FDA-approved inhibitors mentioned previously, are being heavily

investigated in combination therapies with radiation in numerous types of cancer (Table 1). LY2606368, a CHK1 inhibitor, is also currently undergoing a phase I clinical trial in head and neck cancer in conjunction with radiation, with an estimated completion date set for 2019 (Table 1, clinical trial NCT02555644). However, new CHK1 inhibitors are still being developed and tested under preclinical settings in combination with radiation, such as CCT244747, which when used on p53-deficient head and neck squamous cell carcinoma cells increases radiosensitivity to paclitaxel-based chemoradiotherapy [58]. CHIR-124, SAR-020106 and SB-218078, three more CHK1 inhibitors, have also been shown in preclinical studies to increase radiosensitivity in cells with *p53* deficiencies or mutations [59–61]. WEE1 inhibitors, such as AZD11775 (adavosertib), have also made it to the clinic in ongoing phase I and II trials in combination with radiation (Table 1). Alongside Artemis, DNA-PK, ATM, CHK1 and WEE1, other DDR factors not described in this review are also being investigated clinically in conjunction with radiation (Table 1, last two trials). Although all of these proteins are promising future clinical targets, success in clinical trials will depend heavily on understanding the conditions under which these treatments will have a therapeutic gain.

Future Targets and Conclusion

In the past few years there has been an explosion of new information about the DDR and its involvement in cancer, of which we have only just begun to understand how to use in a clinically relevant setting. Although there have been exciting steps in clinical advancements in the treatment of cancer, and there is a plethora of extensive preclinical data to support clinical application for many of these new therapies, researchers and clinicians alike have much still to uncover and learn, especially in the area of how the DDR contributes to carcinogenesis and tumorigenesis, as well as how DDR pathways can be exploited for better future treatments. As an example, although most current cancer therapeutic targets are DDR kinases, about only 4% of all DDR proteins are kinases, leaving a large field of novel, non-kinase targets that could be targeted. Indeed, new players in DDR are continually being discovered, many of which are not kinases. In our own laboratory we have found two new non-kinase players involved in the DDR: SIRT2 and SAMHD1. SIRT2, a class III histone deacetylase (HDAC), was found to be directly involved in the replication stress response acting as a DDR regulator that leads to ATR activation [62–64]. SAMHD1 is a dNTP triphosphohydrolase and HIV-1 restrictase known to have an association with cancer when mutated. Our laboratory discovered that SAMHD1 functions independently of its dNTPase activity in the HR pathway and can be targeted for radiation and PARPi sensitisation using virus-like particles containing Vpx, a lentiviral accessory protein, that targets SAMHD1 for proteasomal degradation [65]. Continuing research into DDR and its components, as well as the drugs that affect DNA repair function, will lead to further clinical advancements in the prevention of cancer and effective therapies.

Conflict of interest

The authors declare no conflicts of interest.

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