Chemical inhibition of DNA repair kinases as a promising tool in oncology

Kamila Durisova, Barbora Salovska, Jaroslav Pejchal, Ales Tichy

Background. DNA repair pathways play a major role in tumour resistance towards chemo- and radiotherapy. Therefore, inhibitors of specific DNA repair pathways might be advantageous when used in combination with DNA-damaging agents, such as ionizing radiation. This review put particular emphasis on the key DNA repair enzymes: DNA-dependent protein kinase (DNA-PK), ataxia-telangiectasia mutated kinase (ATM) and ATM-Rad3-related kinase (ATR) and their specific inhibitors in the context of radio-sensitization.

Results. We reviewed recent studies on novel and potent inhibitors and found evidence that inhibitors of DNA repair pathways such as small molecule inhibitors could be efficient and selective in tumour cells. Interpretation of recent literature results accompanied with implications for practice and further research are presented.

Conclusions. The prospects of targeting DNA repair enzymes to treat cancer are optimistic, but future work will show if this approach has a significant in vivo efficacy, since we are still waiting for the inhibitor which would pass all phases in clinical trials. In spite of the fact that a number of drugs possess interesting synergy of radiotherapy in vitro, the future use will depend on developing compounds with improved solubility and the serum half-life. Normal tissue toxicity leading to a significant increase of radiotherapy efficiency remains a key question that might be answered only by clinical trials.

Key words: DNA repair; inhibitor; DNA-PK; ATM; ATR; ionising radiation

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INTRODUCTION

Double strand breaks (DSB) are one of the most deleterious lesions in DNA. Unfinished or incorrect DSB repair may lead to a loss of genomic information, genome rearrangement or cell death.1,2 Thus, the repair control is necessary for the maintenance of genomic stability. Three phosphatidylinositol 3-kinase like protein kinases (PIKKs): DNA-dependent protein kinase (DNA-PK), ataxia-telangiectasia mutated kinase (ATM) and ATM-Rad3-related kinase (ATR) coordinate DNA damage response (DDR), specifically cell cycle arrest, cell survival and DSB repair.1,4 Two main pathways are employed in DSB repair: homologous recombination (HR) and non-homologous end joining (NHEJ).

The initiation of HR and NHEJ depends on the phase of the cell cycle. HR requires a complementary segment from the sister chromatid or the homologous chromosome. For that reason, HR is used mainly in the S and G2 phases whereas NHEJ rejoins broken ends together without a homologous sequence, therefore it is predominant in the G0 and G1 phases.3 This carries an enormous risk of creating irrelevant joints and consequently an increasing number of mutations in DNA (ref.3).

At the beginning of HR, the MRE11-RAD50-NBS1 complex provides a single stranded DNA (ssDNA) resection to form 3’ tail. RAD52 binds to ssDNA and cooperates with replication protein A (RPA) to promote an effective binding of ssDNA with RAD51 (ref.8,9). Afterwards, RPA is removed by the BRCA2/PALB2 complex and displaced with the RAD51 protein.7 RAD51 catalyses a strand exchange, by which the damaged DNA gets into the intact homologous DNA duplex and forces out one strand as the D-loop (displacement-loop) (ref.10). The formed molecule contains a hetero-duplex region bound by two branched structures called Holliday junctions, which can migrate and therefore a final product with or without crossing over is formed.11,12

The crucial component of NHEJ is DNA-PK, which consists of DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and DNA end binding proteins Ku70/Ku80 (ref.13). The heterodimer Ku70/80 serves as a DSB sensor and recruits DNA-PKcs to the site of DSB in order to form the active DNA-PK complex.13-17 Once DNA-PKcs is in contact with free DNA ends, it is activated by autophosphorylation at Ser 2056 and Thr 2609 (ref.18,19). Afterwards, DNA ligase IV cooperates with X-ray cross complementing protein (XRCC4) and rejoins broken DNA ends.20

When DSB are formed, a chromatin structure is relaxed permitting intermolecular phosphorylation of ATM at Ser 1981. ATM autophosphorylation causes disorganization of an inactive dimer to an active monomer. Other phosphorylations occur at Ser 367 and Ser 1893 (ref.21,22). ATM phosphorylates a plethora of down-stream targets, which are associated with regulation of the cell cycle, DSB repair and apoptosis, such as BRCA1, p95/NBS1, p53, MDM2, CHK1, CHK2, RAD17, BLM, SMC1, 53BP1 and MDC1 (ref.22,23).
The essential role of ATR is regulation of the cell cycle progression to the G₂ phase via phosphorylation of CHK1 at Ser 367 and 345 (ref.24). After activation, CHK1 is released from chromatin in order to phosphorylate other substrates such as CDC25A phosphatase. Phosphorylated CDC25A is inactive and therefore unable to activate cyclin dependent kinase 2 (CDK2). Thus, it results into the cell cycle arrest24,25. This process is required for correct coordination of DNA replication26.

Nearly two-thirds of all cancer patients receive some type of radiotherapy employing ionizing radiation (IR) which induces DSB. The majority of tumours treated by IR or by chemotherapy are resistant to anti-cancer therapy and the effect of this treatment is attenuated by enhancement of DNA repair processes in tumour cells. The effort to prevent DDR in tumour cells is driven by the fact that DNA repair inhibition leads to accumulation of DNA damage and subsequent induction of apoptosis. Thus, blocking DDR has been proposed as a promising therapeutic strategy for cancer treatment and it is the rationale for using PIKKs inhibition in the context of cancer treatment.

This paper is focused on small molecule inhibitors targeting one of the key kinase groups involved in DNA repair, PIKKs. We bring a comprehensive overview of inhibitors, which can increase cytotoxic effects due to inhibition of DNA repair. These inhibitors have been recently developed and they have been investigated as potential radio- and chemo-sensitizers. Some inhibitors with high IC₅₀ were also involved in this review since they represent the most important milestones in the development of recent ones.

**DNA-PK INHIBITORS**

One of the first developed DNA-PK inhibitors was wortmannin ((1alpha,11alpha)-11-(Acetyloxy)-1-(methoxymethyl)-2-oxaandrosta-5,8-dieno(6,5,4-bc)furan-3,7,17-trione) which is a steroidal fungal metabolite37. Arcaro et al. showed that wortmannin could be used for inhibition of phosphatidylinositol 3,4,5-trisphosphate formation with IC₅₀: 5 nM and also inhibition of phosphatidylinositol 3-kinase (PI3-K) by binding to Lys-802 at the p110 catalytic subunit (inhibition of DNA-PK with IC₅₀: 200 nM) (ref.22,23). Wortmannin was unstable in aqueous solutions. It had the half-life shorter than 5 h in tissue culture medium, therefore, it caused only a reversible growth arrest and cells exited in the G₁ and S phases after 30 hours30,31.

LY294002 (2-morpholino-8-phenyl-4H-1-benzopyran-4-one) is an inhibitor based on naturally occurring flavonoid quercetin32, which is structurally unrelated to wortmannin and which inhibits the p110 unit of PI3-K with IC₅₀: 1.4 μM. It was the first inhibitor with specificity against PI3-K (ref.33). Rosenzweig et al. showed that LY294002 potentiated radiosensitivity and decreased DNA-PK activity, however, ATM kinase was also inhibited by this inhibitor34. It has been also reported that LY294002 was capable to inhibit other kinases such as mammalian target of rapamycin (mTOR), casein kinase II (CKII) and PIM-1 (ref.34,35). Even though LY294002 possessed better stability than wortmannin36, a toxicity profile of this compound did not allow its application in clinical trials37.

OK-1035, which was revealed by high throughput screening (3-cyano-5-(4-pyridyl)-6-hydrazono-methyl-2-pyridone), is a specific inhibitor of DNA-PK with IC₅₀: 8 μM (ref.38,39). Take et al. determined that OK-1035 did not affect the activity of protein kinase C (PKC). CDK2, casein kinase I (CKI) or mitogen-activated protein kinase (MAPK) (ref.39). Nevertheless, it had a low inhibitory ability when p53-wt substrate was used. Stockley et al. synthesized their own OK-1035 inhibitor but with IC₅₀: 100 μM, and thus they evaluated OK-1035 as a weak inhibitor. They also showed that OK-1035 did not affect PI3-K and ATM (ref.40).

Ismail et al. analysed another specific inhibitor of DNA-PK revealed by high throughput screening called SU11752 ((Z)-3-(2,4-diethyl-5-((2-oxo-5-(N-phenylsulfamoyl)indolin-3-ylidene)methyl)-1H-pyrrolyl-3-yl)propanoic acid) with IC₅₀: 0.13-0.028 μM. They used 12 μM and 50 μM concentrations in experiments and compared them to the effects of wortmannin. SU11752 was more specific to DNA-PK and it did not influence ATM or PI3-K in comparison to wortmannin. However, it did not affect the cell cycle progression in a lower concentration, and it also inhibited other PI3-K related kinases. Moreover, SU11752 is bound very weakly to DNA-PK therefore it is unlikely to be used in clinical trials41.

Davidson et al. were focused on IC486241 inhibitor. They observed sensitization of colon cancer cells to irinotecan (topoisomerase I inhibitor) with IC₅₀: 1-2 μM. The concentration of 5 μM was cytotoxic. On one hand, IC486241 inhibited phosphorylation of DNA-PK at Ser2056, but on the other hand it enhanced HR by increasing the level of RAD51 protein. This inhibitor is believed to be the first specific DNA-PK inhibitor sensitizing breast cancer cells to doxorubicin (topoisomerase II inhibitor) (ref.42,43).

The IC86621 inhibitor (1-(2-hydroxy-4-morpholin-4-yl-phenyl)-ethanone) is a methyl ketone derivative of the DNA-PK inhibitor IC60211 (2-Hydroxy-4-morpholin-4-yl-benzaldehyde) with IC₅₀: 120 nM. It exhibited no activity against related protein kinases ATM, ATR, CHK1, nor CDK2. Kashishian et al. reported that IC86621 increased cellular toxicity of etoposide (topoisomerase II inhibitor) and bleomycin44. Allén et al. observed that the inhibitor decreased HR and potentiated radiosensitivity of cells in all cell-cycle stages45.

IC87102 (2-(4-hydroxybenzoyl)-5-(morpholin-4-yl)phenol; IC₅₀: 35 nM) and IC87361 (5-hydroxy-7-(morpholin-4-yl)-2-phenyl-4H-chromen-4-one; IC₅₀: 34 nM) are morpholin derivatives also derived from IC60211 (ref.44,45). Shinohara et al. found out that these inhibitors increased radiosensitivity of tumour cells, tumour microvasculature and prevented tumour growth46. The same group of authors showed that these inhibitors potentiated apoptosis in cancer cells, decreased number of mitotic cells and increased number of cells showing DNA fragmentation46.
Vanillin (4-hydroxy-3-methoxybenzaldehyde) is naturally presented in the pods of Vanilla planifolia, Vanilla tahitensis and Vanilla pompona. Durant et al. reported that Vanillin potentiated the effect of cisplatin in a tumour cell culture model. Vanillin did not influence phosphorylation of CHK2, which correlated with the fact that it affected only DNA-PK. Additionally, its inhibition increased the number of cells containing RAD51/RFI foci after cisplatin co-treatment. It was also shown that vanillin increased cytotoxicity of trichostatin A (class I and II mammalian histone deacetylases inhibitor) (ref.50). However, IC₅₀ of vanillin required for sensitization was higher than IC₅₀ of wortmannin.

LY294002 was used as a template for development of the SF1126 inhibitor ((8S,14S,17S)-14-(carboxymethyl)-8-(3-guanidinopropyl)-17-(hydroxymethyl)-3,6,9,12,15-pentaazaoctadecan-18-oate), NU7026 inhibitor (2-(morpholin-4-yl)-benzo(H) chromen-4-one) and NU7441 inhibitor (2-(N-morpholino-8-dibenzothiophenyl-chromen-4-one) (ref.52).

SF1126 is an inhibitor of all isoforms of PI3-K (ref.53). Ozbay et al. evaluated effects of SF1126 on breast cancer cells. The inhibitor decreased proliferation of the cells, phosphorylation of CHK and induced apoptosis. Mahadevan et al. carried out the phase I clinical trial of SF1126 in patients with solid tumours and B-cell malignancies. SF1126 was well tolerated and did not affect PI3-K activity in the normal tissue. An increase in late apoptosis, a decrease in phosphorylation of AKT and a cleavage of PARP correlating with late apoptosis was apparent.

NU7026, an inhibitor from chromenone library, is a cell permeable, ATP-competitive inhibitor of DNA-PK and ATM, but predominantly affects DNA-PK with IC₅₀: 0.23 μM, IC₅₀ for ATM is more than 100 μM (ref.56,57). Tichy et al. observed the complete growth inhibition of leukemic cells after combination of 10 μM NU7026 and the dose of 1 Gy. The level of p53 protein (and its phosphorylation) was decreased as well as γH2AX phosphorylation and ATM-ATR substrates after caffeine treatment. Moreover, the inhibitor exhibited tumour growth inhibition in multiple solid tumour xenografts. CC-115 is in phase I clinical trials now. The goal is to assess the safety and efficacy of the compound employing advanced tumours unresponsive to standard therapies (recruiting, NCT01353625).

In summary, according to preclinical studies, NU7441, IC66221, IC87361, and also CC-115 are among the promising DNA-PK inhibitors and new clinical trials data are expected.

ATM inhibitors

Caffeine (1,3,7-trimethylxanthine) is a methylxanthine with inhibitory effects on ATM (IC₅₀: 0.2 mM), ATR (IC₅₀: 1.1 mM) and mTOR. A concentration greater than 10 mM is required to suppress DNA-PK or CHK1 (ref.66,67). Sarkaria et al. reported that caffeine did not inhibit CHK1 phosphorylation but it inhibited p53 phosphorylation (Ser 15) and also abrogated the G2/M checkpoint. Blasina et al. also observed inhibition of CHK2 activation. Unlike other publications, which reported the caffeine-induced ATM inhibition and the G2/M checkpoint abrogation, Cortez found surprising hyperphosphorylation of ATM-ATR substrates after caffeine treatment in HCT116 cells and hTERT-RPE1 cells. Moreover, he suggested, although caffeine is an inhibitor of ATM-ATR kinase activity in vitro, it could block the cell cycle checkpoints without inhibiting ATM-ATR activation in vivo.

Hickson et al. identified a new small molecule inhibitor of ATM called KU55933 (2-morpholin-4-yl-6-thianthren-1-yl-pyran-4-one) derived from LY294002 (ref.68) with IC₅₀: 12.9 nM. Interestingly, KU55933 was not able to inhibit UV-induced phosphorylation of H2AX (Ser 139), NBS1 (Ser 343), CHK1 (Ser 345) and SMC1 (Ser 966) but it inhibited these phosphorylations after IR treatment together with phosphorylations of CHK2, MDC1, TOPBP1 or BRCA1 at 10 μM. KU55933 was capable to sensitize HeLa cells towards etoposide, doxorubicin, amsacrine and camptothecin (topoisomerase I inhibitor) (ref.70). Shaheen et al. reported that the compound itself...
An improved ATM inhibitor KU60019 ((2R,6S)-rel)-2,6-dimethyl-N-[5-[6-(4-morpholinyl)-4-oxo-4H-pyran-2-yl]-9H-thioxanthen-2-yl-4-morpholineacetamide) is an analogue of KU55933 with $IC_{50}$: 6.3 nM. Golding et al. showed that KU60019 was more water soluble and 3- to 10-fold more potent than its predecessor KU55933. Moreover, it did not influence other 229 kinases and $IC_{50}$ for DNA-PK and ATR was 270- and 1600-fold higher than for ATM, respectively. The inhibitor was able to inhibit phosphorylations of p53 (Ser 15), H2AX (Ser 139), CHK2 (Thr 68) and AKT (Ser 473) in much lower concentrations after irradiation in comparison to KU55933 (ref.72). In other tests Golding et al. discovered that KU60019 was even 30-100 times more potent than KU55933 and inhibited phosphorylation of p53 (Ser 15) or H2AX (Ser 139) at 300 nM being stable up to 72 h in cell cultures73. Finally, both inhibitors (KU55933 and KU60019) were shown to be capable of transient ATM inhibition74,75.

KU59403 (3-(4-methylpiperazin-1-yl)N-(6-(6-morpholin-4-oxo-4H-pyran-2-yl)thianthren-2-yl)propanamide) is an improved analogue of KU55933 with better pharmacological properties and greater selectivity and potency against ATM with $IC_{50}$: 3 nM. Batey et al. determined that the concentration necessary for chemosensitization is 10-fold lower (1 μM) compared to KU55933. They reported that KU59403 at the concentration of 1 μM was able to inhibit more than 50% of ATM activity and potentiated the cytotoxicity of camptothecin, etoposide or doxorubicin. Furthermore, they also observed tumour growth delay after KU59403 treatment in combination with etoposide in mice. The inhibitor maintained a significant concentration in plasma for a longer time in comparison to KU55933. Nevertheless, when administered to mice, the concentration of KU59403 in plasma rapidly decreased69.

Additionally, there are other inhibitors of ATM e.g. CP466722 (2-(6,7-dimethoxyquinazolin-4-yl)-5-(pyridin-2-yl)-2H-1,2,4-triazol-3-amine) (ref.76) or CGK733 (2,2-diphenvlyl-5,6,7,8-tetrahydrobenzo[3',4']cycloocta[1',2':4,5]thioureido[ethyl]acetamide) (ref.77) and the list is not definitive since in the meantime new inhibitors have been synthesized.

**ATR inhibitors**

NU6027 (2,6-diamino-4-cyclohexyl-methoxy-5-nitroso-pyrimidine) was identified as a CDK2 inhibitor86. Peasland et al. found out that NU6027 was a more potent inhibitor of ATR (IC$_{50}$: 2.8-2.9 μM) than of CDK2 (IC$_{50}$: 10 μM). NU6027 had no effect on phosphorylations of either DNA-PK or ATM at 10 μM after irradiation and was able to potentiate the effect of hydroxyurea (ribonucleotide reductase inhibitor), doxorubicin, camptothecin, temozolomide, cisplatin and IR. The inhibitor decreased the number of RAD51 foci-positive cells and modestly reduced the amount of γH2AX foci after PARP inhibitor (PF-01367338) treatment. It also caused synthetic death in combination with the PARP inhibitor or in XRCC1-defective cells79. Sultana et al. employed EM-C11, EM-

C12 (XRCC1-deficient) and CHK9 cells (wild type). After NU6027 treatment, XRCC1-deficient cells showed a higher mean tail moment in the Comet assay, a higher amount of γH2AX foci, a G$_2$ arrest and a higher amount of early apoptotic cells when compared to CHK9 cells. These data confirmed the relationship between ATR and XRCC1, i.e. synthetic lethality80. Unfortunately, NU6027 is not water soluble, which is a substantial limitation for further usage79.

Schisandrin B (1,2,3,13-tetramethoxy-6,7-dimethyl-5,6,7,8-tetrahydrobenzo[3',4']cycloocta[1',2':4,5]benzol[1,2-d][1,3]dioxole) is a dibenzocyclooctadiene derivative isolated from *Fructus Schisandrae*, which is commonly used in Chinese medicine, with IC$_{50}$ 7.25 μM (ref.81,82). This inhibitor is a mixture of gomisin N and γ-schisandrin which are the diastereomers of each other. Tatewaki et al. revealed that gomisin N was an active form responsible for inhibiting ATR (ref.83). Nishida et al. observed that Schisandrin B alone had no effect on cell viability. This is in contrast to combined treatment with UV-radiation, which caused the G$_2$/M checkpoint abrogation and the decrease in phosphorylations of p53 (Ser 15) and CHK1 (Ser 317). Importantly, this was observed in ATM-deficient cells but not cells with ATR depleted by siRNA82. Schisandrin B also potentiated the effect of doxorubicin84.

Pollard et al. identified VE-821 (3-amino-6-(4-methylsulfonyl)phenyl)-N-phenylpyrazine-2-carboxamide) as a selective inhibitor of ATR (IC$_{50}$: 26 nM). VE-821 was able to inhibit CHK1 phosphorylation (Ser 345) and it potentiated the effect of gemcitabine, camptothecin, cisplatin and IR. Pollard also showed that treatment of prostate cancer cells with VE-821 caused higher cell death in comparison to normal cells85. Vavrova et al. showed that the combination of VE-821 and IR in HL-60 cells resulted in a decreased amount of cells in the G$_1$ phase, increased apoptosis and a higher amount of γH2AX foci, which persisted 72 h after irradiation86.

VE-822 (5-(4-(isopropylsulfonyl)phenyl)-3-(3-(4-((methylamino)methyl)phenyl)isoxazol-5-yl)pyrazin-2-amine) is an analogue of VE-821 with increased potency against ATR (IC$_{50}$: 19 nM) and better pharmacokinetic properties87. Fokas et al. reported that VE-822 was able to enhance the effects of IR and chemotherapy in cancer cells but it did not affect normal cells. VE-822 showed a decrease in phosphorylation of CHK1 at Ser 345 after gemcitabine or radiotherapy. It increased the amount of γH2AX/53BP1 foci but it did not affect the ATM, CHK2 or DNA-PK activity. VE-822 abrogated the G$_2$ arrest in combination with IR and increased the number of early and late apoptotic cells88.

Recently, new ATR selective inhibitors called AZD6738 and AZ-20 (4-(4-[3(R)-3-Methyl-4-morpholinyl]-6-[1-(methylsulfonyl)cyclopropyl]-2-pyrimidinyl]-1H-indole) have been discovered. (ref.89). Jones et al. reported discovery of a new ATR inhibitor AZD6738 with good pharmacokinetics and properties for oral administration86. The inhibitor has been evaluated in three clinical trials. The first one is aimed at assessing the safety, tolerability and appropriate dose of the
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**ATM** = ataxia telangiectasia mutated protein; **ATR** = ATM- and Rad3-related protein; **CDK2** = cyclin dependent kinase 2; **DNA-PK** = DNA-dependent protein kinase; **DNA-PK<sub>CS</sub>** = DNA-dependent protein kinase catalytic subunit; **HBV** = hepatitis B virus; **IR** = ionising radiation; **mTOR** = mammalian target of rapamycin; **PI3-K** = phosphatidylinositol-3-kinases; **TSA** = trichostatin A; **UV** = ultraviolet light; **XRCC1** = X-ray repair cross-complementing protein 1. Where no reference is given, information may be found on the ClinicalTrials.gov website.
Fig. 1. Scheme of DNA repair kinases inhibition. Important biological consequences of DNA repair kinases inhibition are shown. DNA-PK phosphorylates DNA ligase IV and/or XRCC4, which may affect their interactions with Ku and other proteins. Thus, inhibition of DNA-PK abrogates NHEJ and impacts DNA repair similarly to inhibition of ATM, which is a key regulator of HR. ATM is required in the initiation of HR for it phosphorylates number of downstream targets such as H2AX, BRCA1, MRN complex, etc. Therefore, ATM inhibition leads to accumulation of DNA damage, too. Additionally, ATM affects apoptosis and cell cycle progression indirectly via phosphorylation of CHK2 or directly via phosphorylation of transcriptional factor p53. The essential role of ATR is regulation of cell cycle progression to the G2 phase via phosphorylation of CHK1. Additionally, mutual cross-talks and interactions of the given kinases have been proved, too. ATM, ataxia-telangiectasia mutated kinase; ATR, ATM- and Rad3-related protein; DNA-PK, DNA-dependent protein kinase; ATRIP, ATR interacting protein; DNA-PKCS, DNA-dependent protein kinase catalytic subunit; DSB, double strand breaks; HR, homologous recombination; IR, ionising radiation; NHEJ, non-homologous end joining; PARP, poly-(ADP-ribose) polymerase; p53, TP53 tumour suppressor; RPA, replication protein A; ssDNA, single stranded DNA; TOPB1, topoisomerase (DNA) II binding protein 1.

inhibitor. The effect of the inhibitor will be determined in patients with advanced cancer without any anticancer treatment and in patients with advanced cancer, who are treated by radiotherapy (recruiting, NCT02223923). The next clinical study was focused on pharmacokinetics and employed different kind of patients (with CLL, PLL or B cell lymphoma) (completed, NCT01955668). The last one combines AZD6738 with cytotoxic chemotherapy regimens and novel anti-cancer agents e.g. carboplatin (recruiting, NCT02264678).

CONCLUSION

Current DNA-damaging anti-cancer strategies, including chemotherapy and radiotherapy, are often unsuccessful because the response to these therapies varies among individual patients and is affected by a cross-talk of different signalling pathways. It is far beyond the extent of this paper to describe all other pathways, inhibition of which contributes to increased sensitivity towards IR (e.g. apoptotic or NF-κB signalling pathway). Therefore, the authors of this review focused on DDR and mainly on PIKKs, which are also in the centre of their experimental interest.

The reviewed studies, which use small-molecular DNA repair inhibitors, show in vitro as well as in vivo, that these novel and potent inhibitors could be developed into future drugs, which would selectively kill tumour cells exhibiting deficiencies in particular DNA repair pathways. So far, clinical relevance of the DNA repair inhibitors has not reached the one of PARP or other inhibitors, because this group is still waiting for a compound that would pass all phases of clinical trials. In spite of the fact that a number of drugs possess interesting synergy with radiotherapy in vitro, future use will depend on developing compounds with improved solubility and the serum half-life, which would enhance anti-cancer therapy.

The recently ongoing clinical trials such as those with CC-115, NVP-BEZ235 or NK31 are expected to answer the question on single-agent support of radiation therapy and to open opportunities for other promising radiosensitizers.

ABBREVIATIONS

ATRIP, ATR interacting protein; ATM, ataxia-telangiectasia mutated kinase; DDR, DNA damage response; ATR, ATM- and Rad3-related protein; DNA-PK, DNA-dependent protein kinase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSB, double strand breaks; HR, homologous recombination; IR, ionising radiation; NHEJ, non-homologous end joining; PARP, poly-(ADP-ribose) polymerase; p53, TP53 tumour suppressor; RPA, replication protein A; ssDNA, single stranded DNA; TOPB1, topoisomerase (DNA) II binding protein 1.

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