DNA Repair 101 (2021) 103074

Contents lists available at ScienceDirect

DNA Repair

journal homepage: www.elsevier.com/locate/dnarepair

Review Article

The role of DNA damage response in chemo- and radio-resistance of cancer cells: Can DDR inhibitors sole the problem?

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ARTICLE INFO

Keywords:
PARP1
ATM
ATR
DDR
Chemo-resistance
Radio-resistance

ABSTRACT

Up to now, many improvements have been made in providing more therapeutic strategies for cancer patients. The lack of susceptibility to common therapies like chemo- and radio-therapy is one of the reasons why we need more methods in the field of cancer therapy. DNA damage response (DDR) is a set of mechanisms which identifies DNA lesions and triggers the repair process for restoring DNA after causing an arrest in the cell cycle. The ability of DDR in maintaining the genome stability and integrity can be favorable to cancerous cells which are exposed to radiation therapy or are treated with chemotherapeutic agents. When DDR mechanisms are error-free in cancer cells, they can escape the expected cellular death and display resistance to treatment. In this regard, targeting different components of DDR can help to increase the susceptibility of advanced tumors to chemo- and radio-therapy.

1. Introduction

DNA-damaging agents originating whether from endogenous or exogenous resources are known to threat the viability of every cell of our body [1]. Besides to the cellular issues arising from the great number of mutations and genome instability, the lack of proper responses can establish generations of these defective cells and put our whole body in danger [1]. DNA damage response or DDR is a precise mechanism which contains sensing the lesions, establishing signals, and finally initiating repair processes by the means of these signals [2]. During DDR, cell cycle is also affected by the mediators of DDR and is temporarily stopped in order to inhibit the replication of a defective DNA [3]. In some cases, DNA deteriorations are irreparable and thus, cell death is the only option on the table [3].

In addition to normal cells, cancerous cells are also able to use the same mechanisms for their chemotherapy- and/or radiotherapy-induced damaged DNA. Until DDR is working properly in a cancerous cell, DNA damages would not lead to cell death and thus, treatment would not be considered successful [1]. This means that despite all the advantageous impacts of DDR, it stands in the way of overcoming a great challenge in cancer therapy: resistance to our common methods, chemo- and radio-therapy. Recently, a great number of researchers have worked on targeting distinct components of DDR for enhancing the efficacy of cytotoxic treatments [4]. In this paper, we review the process of DDR briefly and explain the role of its key players in decreasing the susceptibility of cancer cells to common therapeutic procedures. Additionally, the usage of DDR inhibitors on different types of cancer would be discussed for giving an insight for the treatment of advanced stages of this

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https://doi.org/10.1016/j.dnarep.2021.103074
Received 15 January 2021; Accepted 12 February 2021
Available online 18 February 2021

lethal disease.

2. DNA damage response

As mentioned before, the first step of DDR is the lesion detection and subsequent protein recruitment which prepares a context for DNA repair through five different pathways: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR) and non-homologous end joining repair (NHEJ) [5]. DDR starts with the activity of an enzyme named poly (ADP-ribose) polymerase 1 or PARP1 which has a tendency to DNA breaks and after its activations provides some protein-protein interactions in order to activate some other ingredients of this process [6]. Notwithstanding the substantial activity of PARP1 in DNA damage sensing, this enzyme is not the only involved protein in this process and in different repair pathways some other proteins also get engaged; for instance, xeroderma pigmentosum group C-complementing protein (XPC) in NER [7], apurinic-apyrimidinic (AP) endonuclease 1 in BER [8], and ATM in double-strand break repair [9].

When the DNA-binding domains of this enzyme are attached to the DNA lesion (independent of its sequence), they go through some structural transformations and thereby, affect the other domains of PARP1 which leads to the transmission of ADP-ribose units from donor NAD^+ to the acceptor protein or even the enzyme, itself [10]. Creating a chain composed of ADP-ribose units (PAR) helps the recruitment and activation of other proteins by the means of non-covalent linkages between their PAR-binding domains and the PAR chain [11]. In contrast to the advantages of PAR, if this polymer is not degraded by PAR glycohydrolase (PARG), DNA damage can be increased as a result of the enhanced accessibility and sensitivity to cytotoxicity [12,13]. Nevertheless, it seems that the importance of PARP1 is more highlighted in the single-stranded break repair (SSBR) [6]; hence, we would define more sensing mechanisms which are dedicated to each repair pathway in following sections:

2.1. Nucleotide excision repair (NER)

NER pathway which has the capacity of repairing helix-distorting DNA deteriorations is performed through either global genome repair (GG-NER) or transcription-coupled NER (TC-NER) [14]. The former one is triggered by a complex composed of three proteins: XPC, RAD23B and centrin 2 (CETN2) and the latter one is initiated by Cockayne syndrome (CS) protein A and B [15,16]. When the lesion detection is completed, the transcription factor II H (TFIIH) complex (which contains ten subunits) is formed in this site for providing a condition for the recruitment of XPA and replication protein A (RPA) [17–19]. Afterwards, two essential endonucleases, XPF–ERCC1 and XPG, which have the duty of incising both ends of the break are present by the help of XPA and RPA [20,21]. After the dual incision, the DNA gap is filled at the hand of a DNA polymerase (which can be δ, ε or κ) and two other proteins known as replication factor C (RFC) and proliferating cellular nuclear antigen (PCNA) [22]. Eventually, two complexes are applied beneficial to joining the repaired ends: (XRCC1)–DNA ligase III (LIG3) complex or flap endonuclease 1 (FEN1)–DNA ligase I (LIG1) complex [23,24].

2.2. Base excision repair (BER)

BER pathway is commonly adopted by a cell in response to deamination, alkylation, and more frequently oxidation of the DNA bases [25]. Interestingly, single-strand breaks are also commonly repaired through this method [25].

DNA glycosylases such as N-methylpurine-DNA glycosylase (MPG) [26], The nei-like 1 (NEIL1) and 8-oxoguanine DNA glycosylase (OGG1) [27] administer the first step of this mechanism: sensing [28]. Afterwards, DNA end processing is managed by the help of APE1 [29], Pol beta [30], and PNKP [31] in order to provide two error-free termini for either Pol beta [32,33] or Pol δ/ε [34] to replace nucleotide(s) in the generated gap. After all, DNA ligation proceeds in a same way as NER [35].

2.3. Homologous recombination (HR)

HR along with NHEJ (which is more common in humans) are two major pathways that handle double-strand break (DSB) repair [36]. MRN complex which is formed by the gathering of MRE11, NBS1, and RAD50 has the most pivotal role in DSB detection [37]. DNA end resection in DSB repair is a bit more detailed than SSB repair and is composed of short- and long-scale phases managed by C-terminal binding protein (CtBP)-interacting protein (CtIP) and exonuclease 1 (EXO1), respectively [38,39]. DNA end resection in this mechanism results in the generation of a single-stranded DNA tail which then, is stabilized by RPA [38]. However, for proceeding the next step RPA should be removed by RAD52 and be replaced by RAD51 [40,41]. For extending the ends of the break, RAD51 should find a homology match by the use of the sister chromosome and then, connect this template DNA to the damaged one [36]. In a similar way as the previous repair pathways, polymerases synthesis an error-free DNA and ligases join the newly generated DNA ends [42,43]. During this process two important protein kinases are activated: ataxia telangiectasia mutated (ATM) is activated by the MRN complex and ATR is activated by RPA [25].

2.4. Non-homologous end joining (NHEJ)

Ku70/Ku80 (Ku) heterodimer is the detector of DSB in this procedure which after binding to DNA is able to recruit a multiprotein complex known as DNA-dependent protein kinase catalytic subunit (DNA-PKcs) [44]. The consequence of the recruitment and activation of this complex is the activation of a group of endo- or exonucleases such as Artemis which is the main enzyme in resecting the DNA ends [44,45]. The last phase of NHEJ, DNA ligation, is possible because of a “sleeve-like” structure which is established around the DNA by XRCC4 and XRCC4-like factor (XLF) to facilitate the performance of ligase IV [46–48]. Noteworthy, DNA gap filling in NHEJ occurs prior to the ligation by the use of Pol μ and Pol λ [49,50].

2.5. Mismatch repair (MMR)

This pathway is commonly used for repairing any mismatches that occur in bases due to replication errors or intermediates of the HR pathway [25]. Base mismatches and deletion/insertions are primarily recognized by two heterodimers: MutSα and MutSβ [51]. In eukaryots, two dimers of the former complex include MSH2 and MSH6 and the dimers of the latter one contain MSH2 and MSH3 [51,52]. In eukaryots, after the lesion recognition, some other proteins named MutL get involved in MMR in order to show the right DNA strand (the nascent one) to exonucleases [53]. The excision process is performed afterwards by the help of PCNA and EXO1 which are recruited to the damaged site by MutL complex [25,54]. Eventually, polymerase δ and LIG1 fill the gap in the DNA and complete the MMR process [54].

3. DDR and radiotherapy failure

In general, radiation therapy is mostly known for causing base modifications and DNA breaks; although, DSBs seem to be the most important consequence of this treatment [2].

3.1. NHEJ and HR

14-3-3σ is a member of the "14-3-3" protein family which its impacts on inducing invasion, EMT, and radio-resistance is of interest [55]. Recent investigations indicate that this protein is the bridge between DDR and radio-resistance. NHEJ is the major pathway which is prone to

be affected by 14-3-3σ by the agency of elevating the expression levels of PARP1 and CHK2 [56]. In addition to affecting the expression, 14-3-3σ also decreases the degradation of PARP1. Overall, the major effect of this protein is"up-regulating NHEJ repair while arresting cells in G2/M phase" [56].

CHK2 is a protein kinase which is a mediator in the ATM-dependent signaling and cell cycle arrest after ionizing radiation (IR)-induced DNA break. CHK2 executes its effects on cell cycle checkpoints through some proteins such as Cdc25, E2F1, BRCA1 and more importantly p53 [57,58]. Takai et al. [59] are another group of researchers that demonstrated the important role of CHK2 in radiosesitivity. They found that CHK2 not only regulates the activity of p53 in transcriptional levels but also stabilize this tumor suppressor protein. They also revealed that after IR exposure to mice, apoptosis and G1/S arrest are impaired in the absence of CHK2 [59]. This suggests that despite CHK1, CHK2 inhibitors cannot be used in cancer patients for increasing the treatment efficacy. BRCA1 and 2 are two other proteins, which are responsible for both DNA repair and cell cycle control, are possibly causing radio-resistance [60]. BRCA1 is a key player in DSB repair which binds to CtIP and is able to switch the repair pathway from NHEJ to HR [61]. BRCA2 is also engaged in DSB repair and assists RAD51 to be replaced with RPA on the ssDNA in the HR pathway [62]. Additionally, BRCA1 is also able to increase radio-resistance by switching NHEJ to HR; this happens because NHEJ is an error-prone process which despite HR can increase genome instability in cancer cells [63]. Eenestos et al. [64] worked on BRAC1 and 2 women carriers and indicated that radiosensitivity is more observed in patients who carry the mutated versions of these genes.

ATM and ATR are also helping the failure of radiotherapy failure:

ATM induces radio-resistance mainly through zinc finger E-box binding homeobox 1 (ZEB 1) by stabilizing it and thereby, stabilizing CHK1 [65]. ZEB1 is essential for radio-resistance because of its regulatory effects on EMT. Interestingly, some parts of the ZEB1 function are related to CHK1 [65]. Another function of ATM is amplifying the DSB repair through phosphorylating the histone protein H2A.X. H2A.X phosphorylation is substantial because of its role in recruiting MRN complex, MDC1, ATM, and RNF8 [66]. On the other hand, the effect of ATM on checkpoint activation through stabilizing p53 and phosphorylating NBS1 cannot be neglected [67].

Several interesting features of ATR, such as conducting HR pathway, are also defining some parts of DDR roles in establishing radio-resistance in cancer cells [68]. Moreover, stalled replication fork stabilization, activating the intra-S checkpoint, administering the replication origin firing, and the activation of G2/M checkpoint are some other functions of ATR which their role in radio-resistance cannot be neglected [68]. Furthermore, assessing DNA-PKCS, p53, and PCNA after radiation therapy also showed that these proteins might be engaged in the response of lung cancer cells [69]. However, it seems that Ku70-Ku80 does not have an essential role in radio-sensitivity [69]. Overall, further investigations are required on these proteins. In nasopharyngeal carcinoma, PCNA's influence on radio sensibility is also approved by other researches [70,71].

3.2. BER and NER

In the BER point of view, examinations represent a lower radio-resistance when BER is impaired by some agents such as methoxyamine [72]. 5-Iodo-2′-deoxyuridine (IdUrd) cytotoxicity and radio-sensitization can be enhanced by using BER inhibitors [72]. Considering APE1, there are some contradictory studies regarding the role of this BER component in radiosensitivity; for instance, Herring et al. [73] showed that APE1 expression in cervical carcinoma is related to radio-sensitivity and can be used for predicting the treatment efficacy. Whereas, increased levels of Ape1/ref-1 complex provide a protection against radiation therapy in germ cell tumors [74]. XRCC1 which is involved in the last stage of both BER and NER pathways also has a relation to radio-resistance: XRCC1 mutant cells display more susceptibility cytotoxity after being treated with IdUrd [74]. In addition, polymorphism in XRCC1 gene also results in IR hypersensitivity [75].

4. DDR inhibitors decrease radio-resistance

4.1. Targeting HR and NHEJ

CHK1 is another protein kinase that mediates the DDR-induced cell cycle arrest. Phosphorylation of this protein by ATR results in checkpoint activation by the means of Cdc25A inactivation [76]. In this regard, researchers have worked on utilizing CHK1 inhibitors for decreasing the resistance to radiation therapy; for instance, Engelke et al. [77] MK8776 on pancreatic cancer cells and indicated this inhibitor can reduce the resistance to chemoradiotherapy. However, they highlighted the function of CHK1 through HR pathway in this study. Furthermore, they also revealed that MK8776 increases DNA damage in cancer cells more than normal cells and hence, this inhibitor can be used along with gemcitabine-radiation for patients with locally advanced pancreatic cancer [77].

Due to the parts of ATR and ATM in establishing radio-resistance, numerous trials have tried their inhibitors on cencer cells. Sarkaria et al. and Blasina et al. are two of the first researcher groups which worked on targeting ATR and ATM for affecting the radio-resistance in tumor cells [78,79]. Previously, Gorecki et al. [80] used VX-970 or berzosertib which is a selective small-molecule for preventing the activity of ATR. "The results suggest that VX-970 is indeed a promising anticancer drug that can be used both as monotherapy and in combination with either chemotherapy or radiotherapy strategies" [80]. Toledo et al. [81] demonstrated that besides to the replicative stress, ATR inhibition is even more effective for treating cancer cells which have a p53 deficiency. In this exploration it was also revealed that NVP-BEZ235 which is commonly utilized for limiting the activity of mTOR and PI3K, can also be practical for inhbiting ATR, ATM, and DNA-PKcs [81]. Another study on chordoma represented RAD51 as the essential down-stream part of ATR/ATM signaling which executes the radio-resistant activities of these protein kinases [82]. MRE11 inhibitors are another group radio-sensitizer agents which are also effective on decreasing the resistance to chemotherapy [83]. In a study, pentamidine, a bisbenzamidine derivative, was used on Hela cells and the following was observed: decreased activity of ATM, accumulation of gamma-H2AX, and also reduced accumulation of NBS1 in the DSB site [83].

5. DDR roles in chemotherapy failure

PARP1 is one of the most interesting ingredients of DDR which takes part in chemo-resistance of the cancerous cells through distinct ways. BRD7 degradation is one of the ways by which PARP1 increases survival in tumors [84]. BRD7 is a tumor suppressor protein which has the capacity of impacting epithelial-mesenchymal transition (EMT) and Wnt signaling and inactivating HIF1 alpha/LDHA axis and thereby, inhibiting proliferation, progression, invasion, and metastasis of different cancer cells including breast, prostate, cervical, gastric, and colorectal cancers [85–91]. Hu et al. [84] demonstrated that "BRD7 is directly ribosylated by PARP1 which is then ubiquitinated by a PAR-binding E3 ubiquitin ligase RNF146, leading to degradation of BRD7 and survival of cancer cells". Valanejad et al. [92] find another mechanism of PARP1-induced chemo-resistance in aggressive hepatoblastoma. They find that the PARP1- Ku80/Ku70 complex is responsible for cisplatin-resistance in these cells because of its linkage to aggressive liver cancer domains (ALCDs) which are specific to this cancer [92].

APE1/Ref-1 which is involved in BER process is also related to chemo-resistance; however, it functions through two distinct ways: increasing DDR and resistance and increasing the activity of p53 and sensitivity to therapy. Robertson and colleagues showed that in cases of higher Ape1/ref-1 complex expression, a 2-fold increase in repair

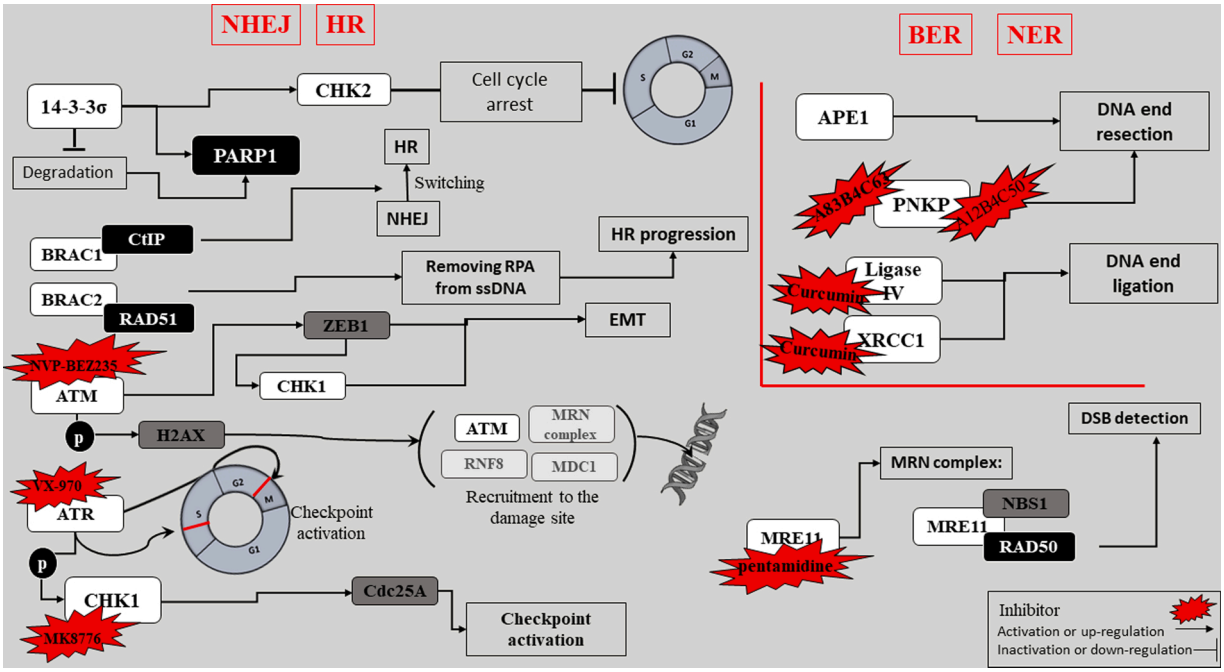

Fig. 1. Schematic representation of the essential components of DDR in radio-resistance and some of the inhibitors of them which are used in clinical trials.

activity in germ cell tumors can be observed which is favorable to Bleomycin-resistance in these cells [74]. By contrast, apoptosis activation after affecting p53 by this complex is approved by other investigations [93,94]. XRCC1 is another BER-related enzyme that its polymorphism is related to altered susceptibility to chemotherapeutic drugs; in a study on 61 colorectal cancer patients, 66% of patients who did not respond to 5-FU/oxaliplatin therapy were carrying a Gln/Gln or Gln/Arg genotype [95]. This suggests the role of XRCC1 polymorphism in impairing BER pathway and thereby, affecting chemo-resistance. ERCC1 is another ingredient of DDR which is involved in the NER pathway and its overexpression is associated with high resistance to platinum-based drugs in epithelial ovarian cancer cells [96].

6. DDR inhibitors decrease chemo-resistance

Due to the substantial role of PARP1 in chemo-resistance, the inhibitors of this enzyme have been extremely considered in cancer therapy. Studies on animal models of different tumors have indicated that PARP inhibitors are capable of sensitizing temozolomide. Other studies have also shown that adding PARP inhibitors to irinotecan results in an enhanced delay in tumor growth [97]. Currently, several clinical trials have been conducted on the role of PARP inhibitors on chemo-resistance of various cancers, such as BRCA1/2 mutated breast cancer, pancreatic cancer, and ovarian cancer [98]. A phase I/II trial has been conducted on the role of veliparib monotherapy as well as the combination of veliparib and carboplatin as a post progression combination therapy in BRCA1/2 mutated metastatic BC. This trial demonstrated that these therapeutic approaches are safe and overall survival of patients was 18.8 months [99]. A phase II trial also reported that patients who received veliparib with carboplatin/paclitaxel show higher overall and progress-free survival compared to patients who received placebo plus carboplatin/paclitaxel. However, this increase was insignificant statically [100]. Using non-coding RNAs is another favorable method in inhibiting the PARP1 functions: Lai and colleagues utilized miR-7−5p on cells with a resistance to Doxorubicin and found that this microRNA is able to impede HR repair through the downregulation of PARP1, BRCA1, and RAD51 [101]. Sun et al.[102] has also shown that the response to PARP inhibitors and cisplatin can be enhanced by miR-506-3p that targets EZH2/β-catenin signal pathway.

A study has reported that Chk1 inhibitor, PF477736, is capable of decreasing colony formation and cell viability of melanoma cells that are resistant to PLX4032 [103]. Moreover, it is shown that PF477736 enhances the sensitivity of PLX4032-resistant cells to PLX4032. Noteworthy, combination of PLX4032 and PF477736 reduces total Chk1 protein level and changes its phosphorylation at various sites in both PLX4032 resistant and sensitive cells [103]. Similarly, Hsu et al. [104] reported that Chk1 inhibition increases cisplatin-induced mitotic cell death through the E2F2 downregulation and caspase 2 activation. In addition, prexasertib and AZD7762 that are Chk1 inhibitors improve the anti-tumor activities of cisplatin and overcome cisplatin resistance in both *in vitro* and *in vivo* models [104].

As it is shown by Kwok et al.[105] using AZD6738 that is an ATK kinase inhibitor leads to the sensitization of TP53- or ATM-defective cells to ibrutinib and chemotherapy. They reported that even at high doses, resistance to monotherapy of bendamustine, fludarabine, and chlorambucil has been evident. Although, addition of 1 mM AZD6738 led in significant sensitization. Furthermore, AZD6738 addition resulted in further sensitization of cells that were already chemo-sensitive [105]. A study has indicated that ATR inhibition results in the sensitization of ovarian cancer cells to the cisplatin, veliparib, topotecan, and gemcitabine. Also, VE-821 that is an ATR kinase inhibitor has shown the ability to further sensitize the BRCA1-depleted cells that were already sensitized by homologous recombination deficiency to veliparib, cisplatin, and topotecan [106]. AZD6738 is another efficient ATR inhibitor which induces cell death, cycle senescence, and the cytotoxicity of cisplatin and gemcitabine in vitro. additionally, in vivo administration of this bio viable inhibitor also enhances the efficacy of cisplatin [107]. In ATM point of view, investigations show that "BRCA1-BER deficient cells are sensitive to ATM and DNA-PKcs inhibitor treatment either alone or in combination with cisplatin and synthetic lethality is evidenced by DNA double strand breaks accumulation, cell cycle arrest and apoptosis" [108].

Boccard et al. [109] demonstrated that targeting ercc1, ercc2, pnkp, and mutyh bi siRNAs leads to the sensitization of cancer cells to chemotherapy which, in turn, increases cell death by up to 25 %. Another paper reported that inhibition of ERCC1-XPF structure-specific endonuclease can be used to overcome chemoresistance. This study showed that ERCC1-XPF-binding inhibitors suppress the Nucleotide

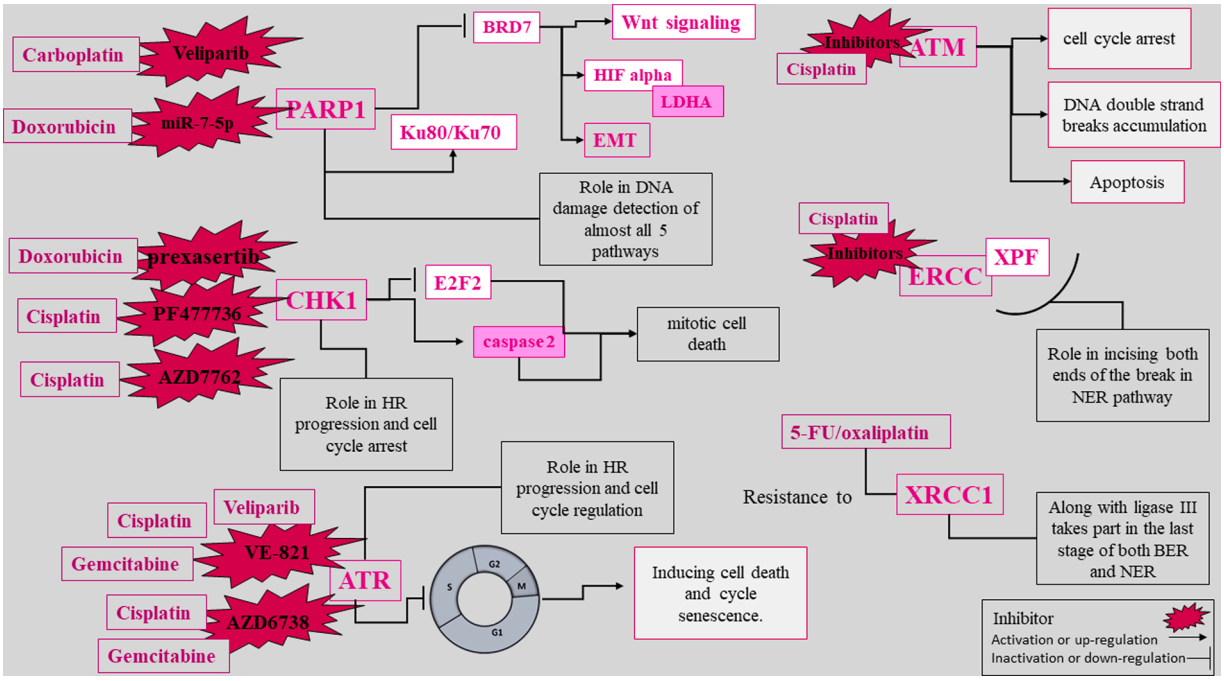

Fig. 2. Schematic representation of the essential components of DDR in chemo-resistance, their inhibitors, and the drugs to which they cause resistance.

Excision Repair, sensitizing melanoma cancer cells to cisplatin. Furthermore, it is indicated that these inhibitors do not sensitize cells that are Nucleotide Excision Repair-deficient [110]. Using non-coding RNAs is another favorable method in inhibiting the PARP1 functions: Lai and colleagues utilized miR-7−5p on cells with a resistance to Doxorubicin and found that this microRNA is able to impede HR repair through the downregulation of PARP1, BRCA1, and RAD51 [101].

7. Conclusions

Notwithstanding the improvements in the field of cancer and the establishment of novel methods such as immunotherapy, gene therapy, and using nanocarriers, still, resistance to therapy is one of the most complicated and effortful obstacles in the way of excluding cancer from the list of leading causes of death. DDR is a set of mechanisms by which a damaged cell sustains its genome stability and integrity along with its survival and viability. As much as these mechanisms are beneficial for every cell of our body, they can be disservice when it comes to cancer therapy. This suggests that targeting the components of DDR is a promising method in this field for enhancing the efficacy of common methods including chemo- and radio-therapy.

As we reviewed in this paper, PARP1, ATM, and ATR are some of the resistance-related proteins involved in DDR which are considered great candidates for being targeted in diverse types of cancer (summarized in Figs.1 and 2). Recently, using DDR inhibitors for cancer treatment has attracted the attention of clinicians and it is expected that in the coming years, this method would be utilized in a greater scale specially for patients who are suffering from an advanced-stage cancer.

Funding

Not applicable.

Availability of data and material

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

Not applicable.

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