DNA Damage Response And Cancer Treatment

Ajithkumar A, Dishon Besleyal S, Abinash R, Saranya Shanmugapriya

Department of Pharmacy Practice, RVS College of Pharmaceutical Science, Sulur, Coimbatore, Tamil Nadu, India.

Corresponding author: Saranya Shanmugapriya
E-mail: saranya_pharm@rvsgroup.com
Doi: https://doi.org/10.5281/zenodo.15569149
Received: 25 April 2025
Accepted: 12 May 2025

Abstract:

DNA damage is a double-edged sword in cancer cells. Where DNA Damage response is deficient to undergoing DNA repair in tumor cells ie; deficiencies of DDR proteins, DNA damage response inhibitors drugs act as anticancer effectiveness that have more potent to kill cancer cells. Designing specific inhibitor to targeting in DNA repair pathway. There are several proteins and their inhibitors being developed and under preclinical and clinical trials. Here might be useful in multiple myeloma, lymphoma, proliferative disorder, head and neck squamous cell carcinoma, breast cancer, ovarian clear cell carcinoma, cholangiocarcinoma and high-risk neuroblastoma likely few types of cancer included in this study. This will carry some of evidence and points regarding resistance in chemotherapy and radiotherapy during utilization DDRinhibitors. Finally, we conclude that emerging DDR Inhibitors which are under clinical trial are beneficial and improves therapeutic outcomes.

Keywords: DNA Damage Response, DNA repair, DDR Inhibitors, PARP, ATM

INTRODUCTION:

DNA damage responses are crucial for maintaining the genome stability. The cells are constantly exposed to the DNA damage from various source including ionising radiation, replication error, UV radiation, cellular metabolism and oxidative stress. The factors that cause single strand break, and double stand break of DNA. To repair single strand breaks, pathways like mismatch repair (MMR), base excision repair (BER), Nucleotide excision repair (NER) are activated. On other hand homologous recombination (HR) and non-homologous end joining(NHEJ) pathways are activated for repairing double strand breaks. These repair pathways provides accurate DNA repair and promotes to abnormal cell apoptosis (Programmed cell death). In this we will discuss current trend and improvements in DNA damage response inhibitors use in cancer therapy. Main role of Micro RNA involved in DDR have major impact in targeting DDR in repair pathway. Some important points related to DDR like trigger of ALPcS4-PDT, use of inhibitors in haematological malignancies, involved intregrinsalpha4beta6 signal activation, few modern DDR inhibitors in Head and neck squamous cell carcinoma and Melanoma and combination therapy in cholangiocarcinoma. Even though some evidence showed useful one, we need supporting evidence of DDR inhibitors in Ovarian cell carcinoma.During chemotherapy and radiotherapy in cancer treatment it may induce some cytotoxicity and resistance to DDR inhibitors. It is major challenge to increase therapeutic outcomes in cancer patients. Further studies must evaluate How to overcome this resistance when it happens? By identifying specific target in DDR, to reduce toxicity and improves outcomes.

1. CURRENT TRENDS IN CANCER THERAPY:

1.1Advances in application of DDR inhibitors

Cc-115 is targeting both DNA-PKcs and mTOR exhibited well tolerated and likely groundbreaking therapy for cancer in phase1 trial (NCT01350625). But inhibiting DNA –PKcn cause side effects and affects normal tissues and cells due to its crucial role in DDR and repair mechanism. Future development methods by use of combination might be promote beneficial effects. It will be increases when produce less toxic DNA –PKcs Inhibitors which must be selective and efficacious to gain good therapeutic benefit.[1]

PARP inhibitors are useful one to enhancing therapeutic effectiveness of these treatments by stimulating synthetic lethality in DNA damage which also sensitize cells to chemotherapy and radiotherapy. Conclude that PARPi use as alone or in combination is therapeutically beneficial one.[1]

Another dual actions drugs to inhibit both ATM & ATR, combined drugs to be provide rationale drug use. Now ATR/ATM inhibitors have been approved for clinical use. Additionally, WEE1 inhibitors are now enrolling phase-1 clinical trial with a hope to be positive outcomes.[1]

2.Key molecular DNA damage response to radiation

Double strand break initiated by irradiation are cause severe lesion by chromosomal translocation, mutation and deletion occur. NHEJ function during G1/S/G2 Phase and HR active inly in S/G2 phase. 53BP1 is one of key factor and RAD51 to repair the lesion by use of template – sister chromatid .53BP1 managing and collecting protein to ATM phosphorylation such as SHIELDIN COMPLEX, R1F1& PTIP.[4] Additionally, CDK phosphorylates CtIP at Thr847and Ser327. Similarly, ATM is key regulation their G1/S/G2 checkpoints.

3.ROLE OF MiRNA IN DDR:

The role of Micro RNA in DNA damage response is explicated from three aspects. MicroRNA regulation on cell cycle, DNA damage repair and apoptosis [10]. The microRNA manages G0\G1 phase, G1 phase progression and G2 /M phase. Likewise, MiRNA regulate DNA damage repair which involves repair of DNA SSBs, Repair of DNA DSBs. MiRNA controls Apoptosis, one leads to promote apoptosis, here specific targets of MiRNA involved and another leads to inhibits apoptosis but here it is associated with multiple pathways.[10]

4.DNA DAMAGE RESPONSE IN CANCER CELLS

4.1DNA Damage response triggered by AlPcS4Cl-PDT

By application of Muse cell analyser, DNA damage response, protein ATM and H2A X was examined by Muse Multicolour DNA damage kit, Here the way the Co expression of ATM andH2ax cells in control and ALPcS4Cl

- PDT treated oesophageal cancer cells , indicating via DNA double strand break and ATM pathway by promoted DNA damage response[3].

4. Researching DDR inhibitors in haematological Malignancies

Several clinical trials Are currently in progress in assessing DDR inhibitors in haematological malignancies. In development of DDR inhibitors, innovative one PARP inhibitors. Here some clinical trials like HRR (Targeting ATR), NHEJ (Targeting DNA –PK), Targeting CHK1, BER (Targeting PARP). In. Combination with Cytotoxicor targeted agent or monotherapy by use of ATR Inhibitors were under investigation.[2]

4.3Integrin alpha6beta4 signal in DDR pathway

In assessing already knows that breast cancer cells are sensitize to cisplatin when integrin alpha6beta4 signals through DNA Damage response pathway. By use of statistical analysis like two tailed or one tailed unpaired student t- test, found outcomes includes integrins alpha6beta4 signals encouraged ATM-p53-53BP1 activation and organised P53and 53BP1 with chromatin were response to treatment using cisplatin & mutant p53 facilitates it. It also induces NHEJ and reduces HR in tolerance to cisplatin. Essential one for improving 53BP1 phosphorylation by DNA-PK. [8]

4.4Modern DDR Inhibitors in HNSCC

Novel therapeutic strategies targeting DDR Pathway in HNSCC. Relevant clinical benefits in various cancer include HNSCC, here multiple PARP inhibitors including Niraparib, veliparib,Talazoparib and Olaparib. And another ATM and ATR inhibitors are under clinical trials as BAY 1895 344 & M6620. DNA –PK inhibitors like M3814 and CC-115 and WEE1 inhibitors as MK-1775 were also in clinical trials it may use in alone or combined with other treatment in HNSCC.[9]

4.5Treating Melanoma with Groundbreaking DDR inhibitors

We already having preclinical proof of anti-tumor effects and cytotoxic effects in treating Melanoma. Recently new compound AZD2461 in target PARP under preclinical studies.[11] Some combination drugs target PARP like olaparib+pembrolizumab, talazoparib+nivolumab(Phase II) ,Veliparib+Paclitaxel+carboplatin(phase I) currently ongoing clinical trials in melanoma cancer. CHK1 is key controller of DDR pathway especially regulate starting point of firing, to bypass DNA breakage, maintaining cancer cells existence under replication stress.Here some of inhibitors (AR323,AR678,GNE-323 and GDC-0575) in Xenograft models having both invitro and in vivo. WEE1 inhibitors – assessing efficacy and acceptability in patient with melanoma malignancies both in combination with drugs (nct04158336) or use as single agent. ATR inhibitors in melanoma obtained a cytosolic DNA fragment from unrepaired DNA damage promoted by ATR inhibition, react and lead to triggering of cGAS- STING signalling. Further studies ongoing use synergistically with radioimmunotherapy.[11]

4.6Findings and Predictions of DDR Inhibition based combination therapy in CCA

To identify CCA most used specification to represent, is presence of mutation in BRCA gene. For therapeutic response of PARPi in CCA were recognised by using predictive biomarker as BRCA Status and it also used in several DDR targeting molecules [12]. There is presence BET proteins (BRD2, BRD3, BRD4, BRDT) and prevents interaction between acetylated histones and BET protein. By improving inflammation condition through DDR inhibition, selected CCA patients with their specific immune level might promote therapeutic intervention to immunotherapy. When alternative and novel strategy might combine DDR inhibitors with antifibrotic drugs. It is blocking activity of VEGFC, EGFR, VEGFA, PDGFR3 and VEGFA, which interprets as single agent in preclinical settings.[12]

4.7Supporting evidence of DDRI IN OCCC

HR deficient and HR competent are categorised as panel of 12 OCCC cell lines, this is assessing RAD51 foci formation it happens when DNA double strand breaks occur in existence of ionising radiation.[14] When there is presence of HR DNA repair deficient in OCCC cells it indicates loss of PTEN function. Some evidence showed

that many types of cancer include colorectal cancer, PTEN undergoes essential role in it and shows polymorphism was related with response to neoadjuvant Chemoradiotherpy.PARPi had proven utility in OCCC but effectiveness of remaining DDR targeting approaches in OCCC was still awaited, especially in clinical trials. In future use PARPi combination with other DDR targeting drug may be useful in OCCC.[14]

4.8Medical advancement of DDR Inhibitors in Neuroblastoma

A half decade ago, few PARPi have been endorsed to date like Olaparib, rucaparib, Niraparib for platinum sensitive ovarian cancer treatment, similarly talzenna used for treatment of germ line BRCA mutated and breast cancer. In neuroblastoma if effectiveness is sustained, use PARPi combined with low dose of chemotherapy might be helpful for reducing long term toxicity. [15] Same as ATR inhibitors M6620 have restricted single agent cytotoxicity. But cytotoxic effects of cisplatin and melphalan in cell lines showed potentiated. Uther studies are mandatory to establish in neuroblastoma are ATR inhibition sensitivity showed confer under which molecular abnormalities.CHK1 prexasertib and SRA373 are recently being evaluated in clinical trials. In High neuroblastoma in paediatric patients are often with severe risk as results of increased dose of chemotherapy and relapse of condition is typical.[15] Here recent note to be in High rish Neuroblastoma patient's prognosis still unreasonable poor.

5. RESISTANCE AND CHALLENGES

5.1ncRNAs as controllers of therapy resistance

In tumor chemotherapy and radiation therapy acceptance by targeting changes in DDR is one of important role by ncRNAs (miRNAs,lncRNAs and circRNAs). these affect DNA damage repair and affect the occurrence and growth of tumors. Significant challenges that want to be noticed, translating miRNAs-based strategies into therapeutic usage for cancer treatment. [5] Further developing regulatory framework supports translation if ncRNAs based therapy in clinical practice. Overall, there is beneficial one for promoting clinical and rational use of drugs and pharmaceutical development.

5.2Treatment strategies for managing resistance by use of DDRi

In view of manage resistance, DDR mechanism of cancer treatment resistance as induction of unrepairable genome wide DNA damage leading to cell death.in case of multiple solid tumor use of cisplatin might be results in development of therapeutic failure and chemoresistance.[7] Glioblastomata have standard drug Temozolomide used to treated.in cancer cells, Radioresistant occur which involve HR. for example, another one resistant happened in radiotherapy by overexpression of BRCA1, BRCA2, RPA1 and RAD51 seen in Nasopharyngeal and Hypopharyngeal carcinoma cells. Several resistance mechanisms and try to overcome by use of PARPi, ATM –ATR Complexes and downstream effectors inhibitions and WEE1 and DNA-DPK to re sensitize cancer cells by inhibitions of DDR. Resistance occurs in PARPi by mutations and loss etc...[7]

CONCLUSION:

By achieving more precision and advancement in developing highly selective and effective drugs is helpful to reduce incidence of cytotoxicity. There by future studies promotes and improves awareness of studies undergoing in DNA Damage response in cancer cells in response to any chemotherapy, radiotherapy and immunotherapy as well. As induced specific target in DNA repair pathway to enhanced therapeutic outcomes and use combination

with other low dose chemotherapy is beneficial to us, several biomarkers with great therapeutic intervention and by essentially expanding patient population that benefits from DDR inhibitors.

REFERENCES:

1. Qian J, Liao G, Chen M, Peng R-W, Yan X, Du J, Huang R, Pan M, Lin Y, Gong X, Xu G, Zheng B, Chen C and Yang Z (2024) Advancing cancer therapy: new frontiers in targeting DNA damage response. Front. Pharmacol. 15:1474337. doi: 10.3389/fphar.2024.1474337

2. De Mel S, Lee AR, Tan JHI, Tan RZY, Poon LM, Chan E, Lee J, Chee YL, Lakshminarasappa SR, Jaynes PW and Jeyasekharan AD (2024) Targeting the DNA damage response in haematological malignancies. Front. Oncol. 14:1307839. doi: 10.3389/fonc.2024.1307839.

3. Didamson OC, Chandran R and Abrahamse H (2024) Aluminium phthalocyanine-mediated photodynamic therapy induces ATM-related DNA damage response and apoptosis in human oesophageal cancer cells. Front. Oncol. 14:1338802. doi: 10.3389/fonc.2024.1338802.

4. Zhang C, Liu J, Wu J, Ranjan K, Cui X, Wang X, Zhang D and Zhu S (2024), Key molecular DNA damage responses of human cells to radiation. Front. Cell Dev. Biol. 12:1422520. doi: 10.3389/fcell.2024.1422520

5. Gao Z, Luan X, Wang X, Han T, Li X, Li Z, Li P and Zhou Z (2024) DNA damage response-related ncRNAs as regulators of therapy resistance in cancer. Front. Pharmacol. 15:1390300. doi: 10.3389/fphar.2024.1390300

6. Moon, J.; Kitty, I.; Renata, K.; Qin, S.; Zhao, F.; Kim, W (2023). DNA Damage and Its Role in Cancer Therapeutics. Int. J. Mol. Sci., 24, 4741. https://doi.org/10.3390/ ijms24054741.

7. Jurkovicova, D.; Neophytou, C.M.; Gašparovi´c, A.C.; ˇ Gonçalves, A.C (2022). DNA Damage Response in Cancer Therapy and Resistance: Challenges and Opportunities. Int. J. Mol. Sci., 23, 14672. https://doi.org/10.3390/ ijms232314672

8. Chen M, Marrs B, Qi L, Knifley T, Weiss HL, D'Orazio JA and O'Connor KL (2022) Integrin a6b4 signals through DNA damage response pathway to sensitize breast cancer cells to cisplatin. Front. Oncol. 12:1043538. doi: 10.3389/fonc.2022.1043538

9. Lei H, He A, Jiang Y, Ruan M and Han N (2022) Targeting DNA damage response as a potential therapeutic strategy for head and neck squamous cell carcinoma. Front. Oncol. 12:1031944. doi: 10.3389/fonc.2022.1031944

10. Li Y, Tong Y, Liu J and Lou J (2022) The Role of MicroRNA in DNA Damage Response. Front. Genet. 13:850038. doi: 10.3389/fgene.2022.850038

11. Maresca, L.; Stecca, B.; Carrassa, L. (2022) Novel Therapeutic Approaches with DNA Damage Response Inhibitors for Melanoma Treatment. Cells, 11, 1466. https://doi.org/10.3390/ cells11091466

12. Gönül Geyik, Ö.; Anichini, G.; Ulukaya, E.; Marra, F.; Raggi, C. (2022) DNA Damage Response Inhibitors in Cholangiocarcinoma: Current Progress and Perspectives. Cells, 11, 1463. https://doi.org/10.3390/ cells11091463

13. Li L, Guan Y, Chen X, Yang J and Cheng Y (2021) DNA Repair Pathways in Cancer Therapy and Resistance. Front. Pharmacol. 11:629266. doi: 10.3389/fphar.2020.629266

14. Wong OGW, Li J and Cheung ANY (2021) Targeting DNA Damage Response Pathway in Ovarian Clear Cell Carcinoma. Front. Oncol. 11:666815. doi: 10.3389/fonc.2021.666815

15. Southgate HED, Chen L, Curtin NJ and Tweddle DA (2020) Targeting the DNA Damage Response for the Treatment of High-Risk Neuroblastoma. Front. Oncol. 10:371. doi: 10.3389/fonc.2020.0037110:581217. doi: 10.3389/fonc.2020.581217.