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The Molecular Mechanism of Radiotherapy Induced DNA Damage and Response in Oncology

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Abstract
Radiotherapy is a common cytotoxic treatment for solid tumors. While the primary goal of radiation-drug combinations is to increase the efficacy of destroying tumor cells, it is also vital to lower the toxicity to normal tissue because the effectiveness of therapy is dependent on the difference between efficacy and toxicity. Radiotherapy-induced DNA damage regulates cell proliferation and modifies the cell cycle, eventually triggering apoptosis or additional programmed death pathways. The molecular pathways of reactions to DNA damage are reviewed, with an emphasis on repair mechanisms, therapeutic targets now being studied in clinical trials, and prospective novel targets. A deeper understanding of the DNA damage responses (DDR's) molecular processes, as well as the genetic linkages between the DDR pathways and other cellular pathways, will lead to new treatment possibilities for a number of human disorders, including cancer.
Keywords: Radiotherapy, DNA damage response, Tumor cell apoptosis, Radiation-drug combination therapy, Molecular repair mechanisms

Introduction

Radiation therapy is a form of treatment in which patients are treated with ionizing radiation. The aim of radiation therapy is to give the cancer the desired dose of radiation while delivering as little radiation as possible to the surrounding healthy tissue. Depending on the circumstances, a radiation dose is delivered to the cancer region using brachytherapy, external beam radiation therapy, or a combination of both. The teletherapy equipment, which administer radiation straight to cancer cells from a distance, eliminating them, distributes the radiation dose to cancer [1]. Direct Ionizing radiation-induced DNA damage is caused by charged particle interface with DNA molecules, with DNA double-strand breaks (DSBs) being highly cytotoxic damage [2]. DSBs can be repaired through a variety of processes that help to keep the genome stable and intact which is necessary for cell survival [3]. Classical non-homologous end-joining (NHEJ), homologous recombination (HR), alternative end- joining (alt-EJ), and single-strand annealing (SSA) are unique DSB repair methods [4]. Therefore, there is a crucial essential to advance basic cognitive and diagnostic tests to detect the early effects of radiation effects in order to timely minimize the harmful properties of ionizing radiation [5][6]. In addition, numerous radiation protection agents have been developed and some are in clinical trials [7]. There are several various types of radiation treatment that can be used to treat cancer, including three-dimensional conformal radiation therapy (3D-CRT), which employs special computers to obtain an exact representation of the tumor's size, shape, and position. Despite X-rays, that shed energy along their course, protons deposit the majority of their energy at the end. Proton therapy is used by doctors to treat Tumors while causing as little destruction to healthy tissue as possible [8].

This review focuses on the biological effects of dose and dose rate in radiation therapy, response to RT DNA Damage, DNA repair of RT-Induced damage DNA repair mechanism and cell signaling, and inhibition of kinases Involved in DDR-related cancer survival pathways. To ensure an acceptable dose to the tumor and the lowest possible radiation exposure to healthy tissue, 3D conformal radiotherapy or 3D-CRT refers to procedures based on 3D anatomical data and using treatment areas that are as close as possible are at the target volume including nodal basins. In addition to the concept of conformal dose distribution, clinical objectives such as maximizing the likelihood of tumor control (TCP) and reducing the likelihood of normal tissue complications (NTCP) have been added. Therefore, to achieve the desired clinical effects, 3D-CRT considers both physical and biological reasons. While 3D CRT requires correct dose distribution, it presents many challenges. The biggest limitation is knowing the extent of the tumor. Despite recent improvements in imaging technology, the clinical target volume (CTV) is often not clearly visible. Usually, CTV is not imaged because it depends on the degree of disease invasion. As the name suggests, this can be the total tumor volume (GTV). Therefore, if the CTVs generated on the cross-sectional images do not fully cover the microscopic spread of the disease, the 3D-CRT loses its compliance meaning. IMRT can be used to treat superficial lesions (such as the parotid gland, cervical lymph nodes, and chest wall) that are often treated with electrons. Nevertheless, in situations where electrons present a technically simpler alternative (e.g., skin cancer, whole skin radiation, and superficial breast augmentation), practical considerations can sometimes prevent the introduction of IMRT. In terms of dose compliance, IMRT is like brachytherapy, but radiobiologically it is a separate technique. Therefore, the radiobiological properties of brachytherapy and the external beam as well as technical or dosimetric factors must be considered when deciding between IMRT and brachytherapy. Due to changes in dosing uniformity and dosing rate or dosing ratio (eg. continuous vs. fractionated) the radiation biology of the two modalities is significantly different.

Dose rates in radiation biology and radiation treatment have ranged from a couple of cGy per day to hundreds of Gy in only a fraction of a second [9]. At this spectrum, the number of cells killed by a given dose reduces with decreasing dose, owing to sublethal damage repair. An inverse dosage effect is reported in cell lines, where the efficiency of a particular dose increases but the dosing rate decreases as cells pass by and are kept in the radiosensitive phase G2. Data on cells of human origin have been collected [10]. The biological effectiveness of the radiation depends on the dose rate. Radiation efficacy can be reduced by 5-10% if administration is prolonged by 5-20 minutes, as shown by calculations and measured cell-killing experiments. Cancers having a low a/b ratio and a short half-life must repair sublethal damage [11]. Prostate cancer is more likely to be susceptible to delayed fraction delivery than tumors with a greater A/B ratio and/or longer repair duration. On the other hand, some other investigators showed that the tumors were extremely insensitive to the release of fold fractions. Thus the dose of radiation affects the molecules of Cancer cell dynamically. Point mutations, in-dels, and massive chromosomal rearrangements are only a few of the genetic changes that might affect Tumor suppressor or oncogene function and lead to cell transformation [12]. According to the genetic instability that underpins carcinogenesis, the mutation frequencies listed above have been linked to hereditary and sporadic occurrences of the disease, owing to greater fidelity in the replication mechanism. Given the importance of DNA damage in genetic changes, it is not unexpected that abnormalities in DNA repair pathways are frequently associated with a propensity to cancer.

Response to RT DNA Damage

Since the DNA molecule serves as the building block of all genetic material, protecting both its structure and its function is essential to preserving typical DNA life activity and consistent species traits [13]. In fact, endogenous or external stress can cause strand breakage, base pair alterations, DNA replication mistakes, DNA double-strand deformations, and other types of DNA damage in cells [14]. Numerous exogenous substances, notably some environmental dangers like radioactive ionising radiation and poisonous heavy metals, have been shown to severely harm DNA [15]. Endogenous materials are frequently generated when exogenous elements are metabolised by the body or when a cell is damaged, and the integrity of the cell membrane is lost [16]. There are two ways that DNA damage can happen: directly and indirectly. The chemical bonds in the DNA molecules are broken when endogenous or exogenous substances come into direct touch with the DNA in the direct route, changing the DNA's structure and function [17]. Endogenous stress, such as gene transcription and replication in cancer cells, is being demonstrated to promote genomic instability. Endogenous or exogenous substances indirectly damage DNA by activating by-products like free radicals. An increasing amount of fresh information derived from DDR process investigations has demonstrated that DNA repair, signaling, and repair are compromised. Cancer is tightly related to signaling pathways, cell cycle checkpoints, apoptosis, replication fidelity, DNA replication, and telomeres [18]. The relationship between DNA mutations and cellular carcinogenesis is becoming more and more obvious as a result of these investigations into the strength of DNA molecules and the process of genetic mutation. Genome instability has been demonstrated to encourage carcinogenesis by activating or suppressing a variety of proto- oncogenes and antioncogenes in a cascade reaction. In this respect, TP53 is a well-known tumor suppressor gene, while the EGFR (epidermal growth factor receptor), MYC, and RAS families have all been extensively recognised as proto-oncogenes [19]. Therefore, cells have evolved a series of signaling mechanisms and post-translational modifications associated to genome stability that evaluate the fidelity of DNA metabolism and limit the buildup of DNA damage in order to lessen the potential of genetic dysregulation of genome stability [20]. For

instance, a number of groups such as ATM (ATM serine/protein kinase), ATR (ATR serine/threonine kinase), and DNA-PKcs (catalytic subunit of DNA-dependent protein kinase) can initiate a chain of signals in mammalian cells. The most Advances in ubiquitination investigation have shown that ubiquitination by numerous enzymes and proteins plays a critical role in regulating cellular homeostasis. In the context of clinical cancer prevention, it is crucial to understand the molecular processes by which cells maintain genome stability and the effects of genomic instability [21]. Mammalian cells have developed a wide range of crucial DNA repair processes and activities to protect against diverse DNA damages. For instance, the pathways for mismatch repair, base excision repair, and nucleotide excision pathways have all been thoroughly characterised. However, aberrant functioning and DNA damage repair mechanisms frequently led to the development of cancer cells. As an illustration, the temporomandibular joint is alliteratively altered between 30 - 50% of the time in numerous cancer cell lines, including mantle cell lymphoma (MCL). These mutations could be linked to cancer treatment resistance. Additionally, genes related to the cell cycle system are essential for protecting cancer cells from the damaging effects of chemotherapy and radiotherapy [22]. H2AX, Mre11-RAD50-NBS1 complex, Ku70/Ku80, MDC1, and 53BP1 are examples of DNA damage sensors that can start damage signals and hence activate DDR. In the study, H2AX may be expressed to monitor the clinical effectiveness of chemotherapy and radiotherapy as well as changes in the susceptibility of cancer cells to anticancer drugs. It can also be expressed to detect the genetic impacts of various harmful substances. Another study looked at DDR processes following treatment for hepatocellular carcinoma and discovered that H2AX expression was elevated [23]. H2AX targeting and H2AX variant function screening have both been suggested as cancer therapies. Other research revealed that Ku70/Ku80 increases linked with chemotherapy and radio resistance in various cancer types. Ku70/Ku80 expression also demonstrated a substantial rise in rectal cancer patients following chemotherapy and radiotherapy. The expression of Ku70 and Ku80 can be used as a molecular cluster to forecast how responsive rectal cancer will be to chemotherapy and radiation [24]. These DDR sensors are still in the early phases of molecular characterisation, in contrast to oxygen sensors, which have received significant study. More research is needed to determine how these DDR sensors function in detecting and signaling DNA damage, cancer progression, and therapy. Studies that look broadly at DDR signaling in the context of carcinogenesis offer valuable knowledge that could be helpful in the creation of specialised cancer treatments. The failure of specific clinical therapy efforts frequently can also be explained by comprehending DDR, which is even more significant. The effectiveness of lung cancer Tumor cells that resist targeted therapy was associated with the activation of the TGF signaling pathway in certain Tumor cells [25]. The expression of DDR-related genes may be suppressed by the activation of TGF, which would reduce the ability of the body to repair DNA, increasing the risk of mutation. Other developments have demonstrated that Tumor heterogeneity can affect the results of targeted cancer therapy [26].

DNA Repair of RT-Induced Damage

Given recent technological developments in the secure delivery of RT and the growing use of novel agents in the clinic, the need for a deeper knowledge of the molecular mechanisms of radiation-induced cell death is more and more pressured [27]. An increasing body of evidence supports the gradual introduction of SABR into ordinary clinical practise and shows that it has outstanding efficacy that is greater than would have been expected by straightforward extrapolation from lesser dosages per fraction. For instance, it has been demonstrated that oligometastatic diseases have a median survival time that doubles and that immunotherapy has a response rate that is more than twice as high, both of which support the theory that the

biology of a tumour's response to radiation differs when a high dosage per fraction is used. In theory, SABR would cause more difficult to repair DNA damage and, because of the shorter total processing time, would inhibit Tumor cell repopulation, although at the expense of diminished cell resorting and reoxygenation within fractions. Finally, a greater knowledge of cell death pathways will allow novel radiosensitizers to be developed [28]. Because many cancer cells rely especially on the G2/M checkpoint, medicines targeting this checkpoint, such as Chk1, Wee1, ATM, and ATR [29], have been developed. HIF-induced revascularization, recurrence, and metastasis can be prevented with hypoxia-modifying therapy [30]. Furthermore, targeting previously overlooked cell death types such as ferroptosis could support a combination of RT and immunotherapy. However, mitotic catastrophe is the most typical scenario for radiation-induced cell death in most solid tumors [31], while normal tissue tends to age following radiation [32]. The significance of cell type may be linked to the cell's state and the function of p53 and ATM. p53 is an important regulator of apoptosis and ageing. Interfacial apoptosis requires intact p53, but disrupting TP53 mutations are associated with higher radioresistance via ageing inhibition [33]. Because most cancer cells either lack normal p53 function or have inactivated their downstream signaling pathways, the G1/S checkpoint is disrupted, and DNA damage repair is therefore dependent on intra-S arrest and G2/M via ATR/Chk1 [34]. As a result, irradiation p53- deactivated cells enter mitosis with unrepaired DNA damage, resulting in mitotic catastrophe rather than rapid apoptosis or senescence [35]. Although modifying p21 or p53 levels can drastically affect the kinetics of cell death after irradiation, it does not always correlate with a loss of replication capacity [36]. Similarly, ATM regulates apoptosis, autophagy, and potentially necroptosis [37] but it is unknown how ATM influences the decision between different cell types. The demise of a cell. The time and type of cell death are also influenced by the phase of the cell cycle during which the radiation occurs. G1-phase irradiated cells divide more frequently and live longer before apoptosis than G2-phase irradiated cells, whereas mid- and late S-phase irradiated cells die without mitosis. Postmitotic apoptosis, on the other hand, seems to be stochastic and varies between cell lines. Protecting the human genome from harm (DNA damage, mutations, DNA strand breakage, links between DNA strands and proteins) provides genome stability and, in turn, chromosomal preservation. The DNA repair process is linked to the type of damage and the cell cycle. DNA repair processes are depicted schematically. It must be acknowledged at this point that the enzymes engaged in individual DNA repair pathways may be replaceable. As a result, categorising DNA repair mechanisms is not absolute [38]. DNA repair heterogeneity was observed in the late twentieth century. First, apurine sites, single-strand breaks (SSBs), and small base distortions in DNA were repaired faster than photoproducts and double-strand breaks (DSBs) in DNA. It was demonstrated preferential repair of active DNA segments over overall DNA repair [39]. Unrepaired DNA damage can cause a cell to die, but it can also cause it to mutate and cause carcinogenesis. DDR is a complex network of proteins that regulates cell cycle and DNA repair. t must be acknowledged at this point that the enzymes engaged in different DNA repair pathways can be replaceable. As a result, categorising DNA repair mechanisms is not absolute [38]. DNA repair heterogeneity was observed in the late twentieth century. First, apurine sites, single-strand breaks (SSBs), and small base distortions in DNA were repaired faster than photoproducts and double-strand breaks (DSBs) in DNA. Hanawalt and his colleagues demonstrated preferred repair of active DNA segments over overall DNA repair [39]. Unrepaired DNA damage can cause a cell to die, but it can also cause it to mutate and cause carcinogenesis. DDR is a complex network of proteins that regulates cell cycle and DNA repair [40,41]. Repair of DNA damage caused by radiation Many types of DNA damage can occur after ionising radiation exposure, triggering repair processes. During BER, DNA glycosylases remove damaged bases, leading to apurine (AP) sites. The AP sites are

then cleaved by apurine endonuclease 1, resulting in SSB. The SSB repair is part of the BER route that fixes SSB [42]. SSB repair is used for short or long periods of time based on the type of injury and the stage of the cell cycle. PARP attaches to SSB, causing self-PARylation and the attraction of BER/SSBR proteins. PARP-1 is thought to be a DNA repair gene regulator in the E2F pathway [43]. While BER repairs the majority of radiation-induced oxidative damage, NER repairs damage that happens in hypoxic conditions. The NER system's DNA helicase ERCC2 heals intra-strand crosslinks caused by genotoxins like as UV light and cisplatin. Ionising radiation has been related to an increased risk of breast cancer caused by the ERCC2 mutation. The development of DSB43 activates three essential PIKK family enzymes, ATM, ATR, and DNA-PK, which triggers downstream signaling cascades to access DNA damage and trigger DNA repair. The presence of DSBs is indicated by the phosphorylation of -H2AX, which drives proteins to repair early-stage radiation-induced bursts.

DNA Repair Mechanism and Cell Signaling

Almost all DNA damage prevents replication, while some can be avoided by error-prone DNA trans damage polymerases. The ability of cells to deal with such a large number of everyday alterations demonstrates the high effectiveness of DNA repair processes. However, DNA damage can result in mutations, structural abnormalities in the chromosomes, cell cycle arrest, cell senescence, and cell death. DSBs are among the most cytotoxic types of DNA damage, accounting for a considerable portion of the cytotoxicity of genotoxic agents and ionising radiation. Additional double-strand breaks, including strand cross-connections, are likewise highly cytotoxic. Cells react to DNA damage by activating DNA signaling and repair mechanisms, which are referred to collectively as DDR. DDR increases cell survival and suppresses cancer by promoting genomic stability, but it also causes cells to die if the damage is too severe. Changes in DDR protein expression or mutation predispose to cancer, determine Tumor response to chemotherapy and radiotherapy, and are at the root of many congenital illnesses, including several kinds of Seckel syndrome, primordial dwarfism, and early ageing syndromes [44]. DDR is a crucial element in cancer cell responsiveness to chemotherapy and radiotherapy, making it an appealing target for enhancing cancer therapy. Since the DDR is an intricate network of interacting/overlapping pathways, cells might respond to alterations in one pathway with compensating modifications in others. Compensatory pathways in the DDR network are key impediments to effective cancer treatment. A greater knowledge of DDR signaling pathways could lead to the discovery of fatal synthetic chemicals that could be used to improve cancer treatment overall and develop personalised medicines. DDR comprises two checkpoint signaling pathways, one devoted to mutated ataxia telangiectasia (ATM), a kinase that response to DSBs, and the other focusing on ataxia telangiectasia and its Rad3 kinase (ATR), that is triggered by single-stranded activation DNA (ssDNA) is activated by resection of the 5'-3' ends of the DSB and the separation of the replication machinery from the MCM helicase at a blocked replication fork. ATM, ATR, and DNA-PKc are PI3 kinase-like kinases (PIKKs) that respond quickly to DSB and replication stress.

EGFR activates Stat3, and phosphorylated Stat3 penetrates the nucleus to enhance c-Myc production, which suppresses p27 [45]. p27 is a cyclin-dependent kinase (CDK) inhibitor that stops cells in the G1 phase of the cell cycle. The researchers reported that decreased p27 expression can affect the cell cycle and make esophageal cancer cells more susceptible to radiation resistant [46]. The EGFR/Stat3/c-Myc/p27 pathway may contribute to ECSC quiescence, according to this study. Signaling NF-κB signaling is activated, which regulates downstream target genes like cyclin D1 and c-Myc, inhibits apoptosis, and promotes Tumor

cell proliferation, invasion, metastasis, and resistance to radiotherapy and chemotherapy [47]. Promotion of the prostaglandin endoperoxide synthase 2 (PTGS2)/NF-B signaling pathway boosts cellular resistance to radiation in glioma. Aurora-A stimulates NF-B activity and boosts the expression of its downstream effectors, including as Mcl-1, Bcl-2, PARP, and caspase-3, in human HCC, decreasing radiation-induced apoptosis [47]. Similar results were seen in breast cancer and melanoma cells, indicating that targeting NF-κB can overcome radiation resistance. By inhibiting the NF-κB signaling system, Tumors may become more sensitive to radiation. In cancer radiation sensitivity is closely related to NF-κB activity, and inhibition of NF-κB signaling pathway may increase radiation sensitivity [48].

Therefore, inactivation of cell death signaling, multiple pro-survival signaling pathways affecting proliferation and conferring anti-apoptotic abilities, play an important role in regulating tumor cell responses to chemotherapy, leading to poor therapeutic outcomes. By comparing the sensitivity of normal and defective p53 tumor cells to cisplatin, it has been shown in several in vitro experiments and clinical studies that the stability and activation of wild-type p53 are crucial for cisplatin-induced apoptosis. Several ovarian cancer patients with normal wild-typep53 expression have been identified. Patients with p53 mutations are likely to respond better to cisplatin. To enhance apoptosis in testicular germ cell Tumors, p53 can upregulate (kill/differentiate) the Fas receptor cluster (CD95)/apoptosis antigen 1. Fas protein expression, on the other hand, is reduced in cisplatin-resistant metastatic colon cancer cells lacking p53 function. The transcriptional stimulation of the Fas/CD95 death receptor pathway by p53 may be a key role in increasing cisplatin sensitivity in p53-positive cancer cells [49]. Many malignancies have increased or high expression of the EGFR family of protein tyrosine kinases, which are produced by the Erb-B2 receptor tyrosine kinase 2 (ERBB2) gene. ERBB2 signaling is mediated by several downstream signaling pathways, notably src homology and collagen (CHS)/growth factor receptor 2 /Son of Seven less and PI3K/Akt1signaling [50]. The PI3K/Akt-1 pathway stimulates the expression of the cyclin-dependent kinase inhibitor 1A protein in cellular homeostasis, whereas ERBB2 overexpression enhances CDKN1A nuclear translocation. Surprisingly, both methods can cause chemo resistance. This study demonstrates that ERBB2 overexpression causes chemo resistance in NSCLC patients. A combination of chemotherapy medications is frequently used in clinical settings to treat cancer patients; however, cancer cells might be resistant to multiple classes of chemotherapy treatments; so, diverse chemotherapy tactics based on the patients' individual genetic background are necessary. PARP drugs, for example, have been designed to treat patients with BRCA1/2 loss, which is synthetically fatal in Tumors lacking homologous recombination (HR). Non-homologous end-joining (NHEJ) is the initial step of DSB repair, which connects damaged ends together without the need for a similar model. HR is another model-directed DSB repair method [51]. This signaling pathway involves many Tumor suppressors, including BRCA1, BRCA2, and ATM. Interstrand crosslinks (ICLs) are forms of DNA damage induced by covalent connections formed between two complementary strand bases that prohibit DNA strand dissociation and inhibit transcription and replication. DNA repair pathways are critical for genome integrity, and understanding how these processes are regulated can help in the development of methods to control cancer development and minimise the risk of cancer progression.

Inhibition of Kinases Involved in DDR-Related Survival Pathways

The PIKK family mutant Ataxia telangiectasia (ATM) is triggered at DNA double-strand breaks (DSBs) and phosphorylates the kinase CHK2 and the Tumor suppressor p53, among many other substrates, to activate the G1/S52 checkpoint. ATM also phosphorylates CHK1 and CHK2 to trigger cell cycle arrest in S or G2/M. Furthermore, ATM phosphorylates

hundreds of additional proteins involved in a wide range of molecular activities like as DNA repair, chromatin structure, transcription, and apoptosis. ATM kinase activity can be suppressed by low molecular weight ATP analogues. KuDOS Pharmaceuticals produced KU55933, a strong and selective ATM inhibitor. AstraZeneca has also recently begun Phase I clinical studies using a different TMJ inhibitor, AZD0156, either alone or in conjunction with the PARP inhibitor olaparib, implying that drug-like TMJ inhibitors may be created. DNA- PK is a PIKK that comprises of a DNA-dependent protein kinase catalytic subunit (DNA- PKcs) and a Ku70/Ku80 heterodimer. DNA-PKcs is required for the canonical non- homologous end-splicing pathway (NHEJ). NHEJ is necessary for DSB repair as well as antibody diversity production in fully developed B cells (class switching recombination (CSR)). The NHEJ creates and repairs scheduled DPOs during the CSR. The NHEJ failure caused by DNA-PKcs mutations most likely contributes to the radiation hypersensitivity and immunodeficiency found in DNA-PKcs mutant patients [52]. Increased DNA-PK expression, on the other hand, is linked to radiation resistance in cervical and prostate cancer [53]. DNA- PKc has been linked to telomere maintenance, transcription, and a variety of other processes in addition to its participation in NHEJ. This type of ssDNA can result from DSB nucleolytic processing of DNA, and it can also be found at a stopped replication fork when the action of the replicative DNA helicase (MCM complex) separates from the activity of the DNA polymerase machinery [54]. The AstraZeneca ATR AZ20 Inhibitor Toolkit, like the Vertex ATR Inhibitors, is a selective ATP-like ATR inhibitor with an in vitro IC50 of 5 nM. In clinical trials, AZD6738 is an orally accessible AZ20 analogue with outstanding pharmacokinetic and solubility properties [55]. DDR is essential for Tumor suppression and encompasses key targets that give therapeutic resistance to radiation and chemotherapy. Some DDR inhibitors are so toxic that their use during protracted fractionated radiotherapy raises safety issues. ATM and ATR inhibitors are also being investigated for synthetic lethal effects in combination with PARP1 inhibitors [56]; such combinations may improve radiation therapy. The PI3K/AKT/mTOR pathway not only inhibits apoptosis and promotes cell proliferation, but it also acts with DDR to induce HR and NHEJ. PI3K/AKT/mTOR inhibitors make Tumor cells more sensitive to PARP1 inhibitors and radiotherapy [57]. Most cervical malignancies are caused by HPV, which modifies DDR to impart treatment resistance, and DDR inhibitors are being researched to enhance cervical cancer outcomes [58]. In response to DSBs caused by radiation or chemotherapeutic drugs, ATM, ATR, and Chk1 signaling alter PD-L1 expression [59]. TMJ arrest following radiotherapy increased Tumor immunogenicity and sensitivity to PD-L1 immune checkpoint inhibition in preclinical trials [60].

Conclusions

DDR signalling, DNA repair, and replication mechanisms are all intricately linked and essential regulators of genome integrity, replication, and cell viability/proliferation. It implies that medications addressing DDR and DNA repair factors could be particularly successful against cancer, especially if they take advantage of the findings. cancer-specific synthetic lethality. Unfortunately, these systems are also important in normal cells, and DNA repair and DDR inhibitors, especially when delivered systemically, can cause intolerable damage to normal tissues and jeopardise the patient's quality of life in the short and long term. and perhaps reduced life expectancy as a result of organ failure, faster Tumor growth, or secondary malignancies. A recent study found that the temporomandibular joint neutralises harmful NHEJ at a collapsed replication fork, which is an example of this delicate equilibrium. It suggests new fatal synthetic techniques for treating malignant Tumors of the temporomandibular joint. However, it is possible that blocking ATM increases NHEJ- mediated misrepair of individual DSBs during (treatment-induced) replication stress. This

could destabilise the DNA, causing surviving cancer cells to proliferate faster or triggering subsequent malignancies. Defects in the DNA damage repair process could make cancer cells more susceptible to cytotoxic medicines. DDR drugs have been clinically verified in small patient populations, and other combined techniques to blocking the multiple pathways cancer cells utilise to survive are being investigated. Indeed, an improved knowledge of the mechanisms underlying radiation-induced DDR, as well as the specific functions of key genes and proteins in DDR signaling pathways, as well as their interacting partners, is critical for clinical detection of new targets for radiation interventions and cancer treatment development. The therapeutic landscape of anticancer medicines targeting DDR encompasses a wide range of cancer types and has rapidly diversified to include inhibitors of other major DNA repair mediators. While the major purpose of combining radiation treatment and pharmaceuticals is to increase efficiency in killing cancer cells, lowering toxicity to normal tissues is equally critical, as therapeutic effect is dependent on the difference between efficacy and toxicity. Furthermore, novel molecular targets necessitate further clinical trials for evaluation.

References

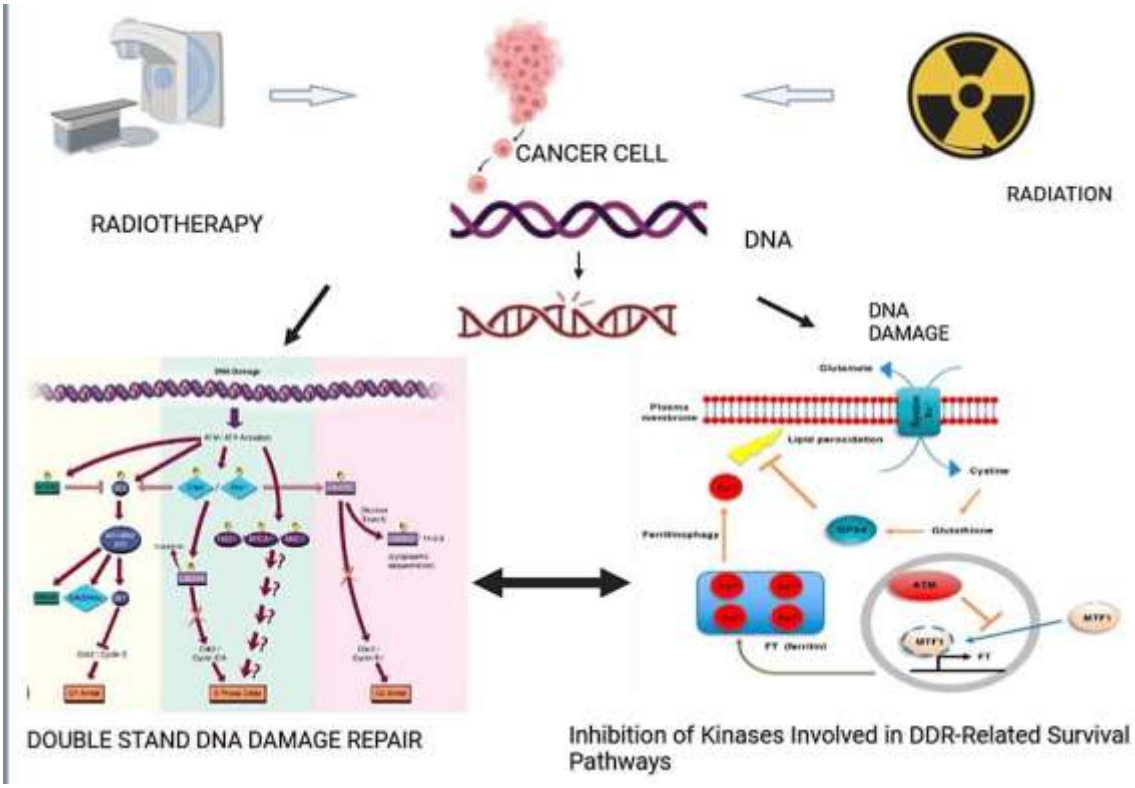
1. Abraham, Z.H., Symonds, N. (1990). Purification of overexpressed gam gene protein from bacteriophage Mu by denaturation-renaturation techniques and a study of its DNA-binding properties. *Biochem. J*. 269, 679-684.
2. Liu, Y.P., Zheng, C.C., Huang, Y.N. (2021). Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. *Med. Com.* 3, 315-340.
3. Rodgers, K., McVey, M. (2016). Error-prone repair of DNA double-strand breaks. *Journal of Cellular Physiology*, 231(1), 15-24.
4. Haber, J.E. (2014). Genome stability. In DNA repair recombination. New York: Taylor and Francis Group. 1-28.
5. Jain, S. (2021). Radiation in medical practice & health effects of radiation: Rationale, risks, and rewards. *Journal of Family Medicine and Primary Care*, 10(4), 1520-1524.
6. Jowsey, P.A., Doherty, A.J., Rouse, J. (2004). Human PTIP facilitates ATM-mediated activation of p53 and promotes cellular resistance to ionizing radiation. *J. Biol. Chem.,* 279, 55562-55569.
7. Hevener, K.E. (2018). Recent developments in topoisomerase-targeted cancer chemotherapy. *Nat. Rev. Cancer*. 8, 844-861.
8. Lieber, M.R. (2010). The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. *Annu. Rev. Biochem*. 79, 181-211.
9. Mansoori, B., Mohammadi, A., Davudian, S. (2017). The different mechanisms of cancer drug resistance: a brief review. *Adv. Pharm. Bull*. 7, 393-348.
10. Brooks, A.L., Hoel, D.G., Preston, R.J. (2016). The role of dose rate in radiation cancer risk: evaluating the effect of dose rate at the molecular, cellular and tissue levels using key events in critical pathways following exposure to low LET radiation. *Int. J. Radiat. Biol.* 92(8), 405-426.
11. Dainiak, N. (2002). Hematologic consequences of exposure to ionizing radiation. *Exp. Hematol.*, 30(6), 513-528.
12. Osborne, C., Wilson, P., Tripathy, D. (2010). Oncogenes and tumor suppressor genes in breast cancer: potential diagnostic and therapeutic applications. *Cold Spring Harbor Perspectives in Biology*, 1, 003236.
13. Thiery, J.P. (2002). Epithelial-Mesenchymal Transition in Cancer: A Historical Overview. *Nat. Rev. Cancer*, 2, 442-454.

14. Miziak, P., Baran, M. (2011). Estrogen Receptor Signaling in Breast Cancer. *Nat. Rev. Cancer*, 11, 597-608.
15. Ohiagu, F.O., Chikezie, P.C. (Ed.). (2021). Human exposure to heavy metals: toxicity mechanisms and health implications. *Medical Science*, 961, 254. doi: 10.15406/mseij.2022.06.00183.
16. Martin, S.A., Hewish, M., Lord, C.J., Ashworth, A. (2010). Genomic instability and the selection of treatments for cancer. *J. Pathol*., 220(2), 281-289.
17. Khan, A., Ashraf, M. (2008). Exogenously applied ascorbic acid alleviates salt- induced oxidative stress in wheat. Environ. *Exp. Bot*., 63, 224-231.
18. Aguilera, A. (2002). The connection between transcription and genomic instability. *EMBO J*., 21, 195-200.
19. Alexandrov, L.B., Stratton, M.R. (2014). Mutational signatures: the patterns of somatic mutations hidden in cancer genomes. *Curr. Opin. Genet. Dev*., 24, 52-60.
20. Tiwari, V., Wilson, D.M. (2019). DNA damage and associated DNA repair defects in disease and premature aging. *Am. J. Hum. Genet*., 105(2), 237-257.
21. Bischoff, M. E., Shamsaei, B., Yang, J., et al., (2024). Copper drives remodeling of metabolic state and progression of clear cell renal cell carcinoma. *bioRxiv : the preprint server for biology*, 2024.01.16.575895. https://doi.org/10.1101/2024.01.16.575895
22. Bauer, D. E., Harris, M. H., Plas, D. R., Lum, J. J., Hammerman, P. S., Rathmell, J. C., Riley, J. L., & Thompson, C. B. (2004). Cytokine stimulation of aerobic glycolysis in hematopoietic cells exceeds proliferative demand. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*, *18*(11), 1303-1305.
23. Williams, J.S., Lujan, S.A. (2016). Genome-wide mutagenesis resulting from topoisomerase 1-processing of unrepaired ribonucleotides in DNA. *Nature Reviews Molecular Cell Biology*, 17, 350-363.
24. McKinnon, P.J., Caldecott, K.W. (2007). DNA strand break repair and human genetic disease. *Annu. Rev. Genomics Hum. Genet*., 8, 37-55.
25. Caldecott, K.W. (2007). Causes and consequences of DNA single-strand breaks. *Oncogene*, 26, 7717-7719.
26. Hofman, M.S., Emmett, L. (2017). Tumor heterogeneity and therapy resistance: Implications for future treatments of prostate cancer. *J. Cancer Metastasis Tre*at., 6, 12-302.
27. Palma, D.A., Olson, R., Harrow, S. (2019). Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*, 393, 2051-2058.
28. Eswar, N., Webb, B. (2016). Comparative protein structure modeling using MODELLER. *Curr. Protoc. Bioinformatics*, 54(1), 5-6.
29. Macintosh, B., Graham, J.R., Ingraham, P. (2014). First light of the Gemini planet imager. *Proc. Natl. Acad. Sci*., 111(35), 12661-12666.
30. Eriksson, D., Stigbrand, T. (2010). Radiation-induced cell death mechanisms. *Tumor Biol*., 31, 363-372.
31. McKenzie, B., Khazen, R., Valitutti, S. (2023). Greek fire, poison arrows, and scorpion bombs: how tumor cells defend against the siege weapons of cytotoxic T lymphocytes. *Frontiers in Immunology*, 13, 894306.
32. Zamzami, N., Kroemer, G. (2003). p53 in apoptosis control: An introduction. *Oncogene*, 22, 9030-9040.

33. Skinner, E.A., Pitzer, J.R. (2012). Developmental dynamics of student engagement, coping, and everyday resilience. *Handbook of Research on Student Engagement*, 21-44.
34. Sia, J., Szmyd, R., Hau, E., Gee, H.E. (2022). Molecular mechanisms of radiation-induced cancer cell death: a primer. *Frontiers in Cell and Developmental Biology*, 8, 41.
35. Ianzini, F., Bertoldo, A., Kosmacek, E.A., Phillips, S.L., Mackey, M.A. (2006). Lack of p53 function promotes radiation-induced mitotic catastrophe in mouse embryonic fibroblast cells. *Cancer Cell International*, 6, 1-8.
36. Lowe, S.W., Ruley, H.E. (1999). p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. *Cancer Research*, 59, 1391-1399.
37. Chen, W., Zheng, R., Baade, P.D. (2016). Cancer statistics in China, 2015. CA: *A Cancer Journal for Clinicians*, 66(2), 115-132.
38. Tian, C., &Horne, R.N. (2015). Machine learning applied to multiwell test analysis and flow rate reconstruction. In: *SPE Annual Technical Conference and Exhibition.*
39. Ganesan, A., Spivak, G., Hanawalt, P.C. (2012). Transcription-coupled DNA repair in prokaryotes. *Progress in Molecular Biology and Translational Science*, 110, 25-40.
40. Scalise, M., Marino, F., Salerno, L. (2022). From spheroids to organoids: the next generation of model systems of human cardiac regeneration in a dish. *International Journal of Molecular Sciences*, 22(24), 13180.
41. Biau, J., Lapeyre, M., Troussier, I., Budach, W., Giralt, J., Grau, C., Kazmierska, J., Langendijk, J.A., Ozsahin, M., O'Sullivan, B., Bourhis, J. (2019). Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update.*Radiother Oncol*.134, 1-9.
42. Zhang, Y., Rohde, L.H., Emami, K. (2008). Suppressed expression of non-DSB repair genes inhibits gamma-radiation-induced cytogenetic repair and cell cycle arrest. *DNA Repair*, 7(11), 1835-1845.
43. Delaney, G., Jacob, S., Featherstone, C., Barton, M. (2005). The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 104(6), 1129-1137.
44. Kuban, D.A., Levy, L.B., Potters, L. (2006). Comparison of biochemical failure definitions for permanent prostate brachytherapy. *International Journal of Radiation Oncology, Biology, Physics*, 65(5), 1487-1493.
45. Zhu, L., Jiang, M., Wang, H. (2013). A narrative review of tumor heterogeneity and challenges to tumor drug therapy. *British Journal of Cancer*, 108(3), 479-485
46. Garcia, R., Bowman, T.L., Niu, G. (2001). Constitutive activation of Stat3 by the Src and JAK tyrosine kinases participates in growth regulation of human breast carcinoma cells. *Oncogene*, 20(20), 2499-2513.
47. Abukhdeir, A.M., Park, B.H. (2008). P21 and p27: roles in carcinogenesis and drug resistance. *Experimental Review of Molecular Medicine*, 10, e19.https://doi.org/10.1017/S1462399408000744
48. Liu, Y.P., Zheng, C.C., Huang, Y.N. (2021). Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. *Medical Communication*, 3, 315-340.
49. Abraham, Z.H. (1990). Purification of overexpressed gam gene protein from bacteriophage Mu by denaturation-renaturation techniques and a study of its DNA-binding properties. *Biochem J.*, 269, 679-684.
50. Zhang, S.M., Yi-Sun, Borgne, A., Golsteyn, R.M. (2003). The role of cyclin- dependent kinases in apoptosis. *Progress in Cell Cycle Research*, 5, 453-460.

51. Qiu, S., Huang, J. (2021). MRN complex is an essential effector of DNA damage repair. *National Science*, 22(1), 31-37.
52. Cook, J., Nuccitelli, D., Green, S.A., Skuce, A. (2013). Quantifying the consensus on anthropogenic global warming in the scientific literature. Environmental Research Letters, 8:024024. DOI: 10.1088/1748-9326/8/2/024024
53. van Houdt, P.J., Saeed, H. (2017). Integration of quantitative imaging biomarkers in clinical trials for MR-guided radiotherapy: Conceptual guidance for multicentre studies from the MR-Linac Consortium Imaging Biomarker Working Group. *Nature Reviews Clinical Oncology*, 14, 169-186.
54. Chen, B.P., Uematsu, N., Kobayashi, J. (2007). Ataxia telangiectasia mutated (ATM) is essential for DNA-PKcsphosphorylations at the Thr-2609 cluster upon DNA double-strand break. *Journal of Biological Chemistry*, 282, 6582-6587.
55. Liu, L., Chen, X. (2009). Autophosphorylation transforms DNA-PK from protecting to processing DNA ends. *Journal of Clinical Investigation*, 119(1), 91-98.
56. Dylgjeri, E., McNair, C., Mandigo, A.C., Pleiotropic impact of DNA-PK in cancer and implications for therapeutic strategies. *Clinical Cancer Research*, 25(18), 5623- 5637.
57. Nickoloff, J.A., Taylor, L., Sharma, N., Kato, T.A. (2021). Exploiting DNA repair pathways for tumor sensitization, mitigation of resistance, and normal tissue protection in radiotherapy. *Cancer Drug Resistance*, 4, 244.
58. Brandsma, I., Fleuren, E.D., Williamson, C.T., Lord, C.J. (2017). Directing the use of DDR kinase inhibitors in cancer treatment. *Expert Opinion on Investigational Drugs*, 26, 1341-1355.
59. Rafiei, S., Fitzpatrick, K. (2020). ATM loss confers greater sensitivity to ATR inhibition than PARP inhibition in prostate cancer. *Cancer Research*, 80(9), 2094-2100.
60. Torgovnick, A., Schumacher, B. (2015). DNA repair mechanisms in cancer development and therapy. *Frontiers in Genetics*, 6:157.doi: 10.3389/fgene.2015.00157

Appendices


RADIOTHERAPY
CANCER CELL
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DNA
DAMAGE
DOUBLE STAND DNA DAMAGE REPAIR
Inhibition of Kinases Involved in DDR-Related Survival Pathways