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DNA Repair Molecules and Cancer Therapeutical Responses

Yasuko Kitagishi, Mayumi Kobayashi and Satoru Matsuda

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<http://dx.doi.org/10.5772/53532>

1. Introduction

Cells are equipped with the multiple DNA repair mechanisms to deal with DNA damage and transduce the signal downward, which provokes a process to inhibit cell cycle progression and to induce DNA repair [1, 2]. The main DNA damage recognition molecule is ataxia telangiectasia-mutated (ATM), which is a checkpoint kinase that phosphorylates a number of proteins including p53 and BRCA1 in response to DNA damage (**Figure 1**), and thus induce the response to it [3, 4]. Mutations in the ATM have been associated with increased risk of developing a cancer. In addition, it is well known that mutations in the p53 and BRCA1 tumor suppressor genes account for a certain amount of cancers. The p53 protein is a key transcription factor that regulates several signaling pathways involved in the cellular response to genome stress and DNA damage. Through the stress-induced activation, p53 triggers the expression of target genes that protect the genetic integrity of cells [5, 6]. Normal cells show an exquisite balance among these various mechanisms of DNA repair.

Genomic instability is often linked to DNA repair deficiencies. Standard DNA repair pathways available in mammalian cells include homologous repair, nonhomologous end joining, single strand annealing and so on. Those are different pathways that repair DNA double strand breaks (DSBs) [7]. The DNA repair is essential for the survival of both normal and cancer cells. An elaborate set of signaling pathways detect the DSBs and mediate either survival on the DNA repair or apoptotic cell death [8, 9]. The DNA damaging agents for cancer therapies are potent inducers of cell death triggered by the apoptosis. Recent advances in basic science have led to a better understanding of the molecular events important in the pathogenesis of cancer. In the present review, we summarize the function of prominent DNA repair molecules and the tumor suppressor gene products, p53 and

BRCA1 (**Figure 2**), at a viewpoint of carcinogenic DNA damage and therapeutical modulation in cancer.

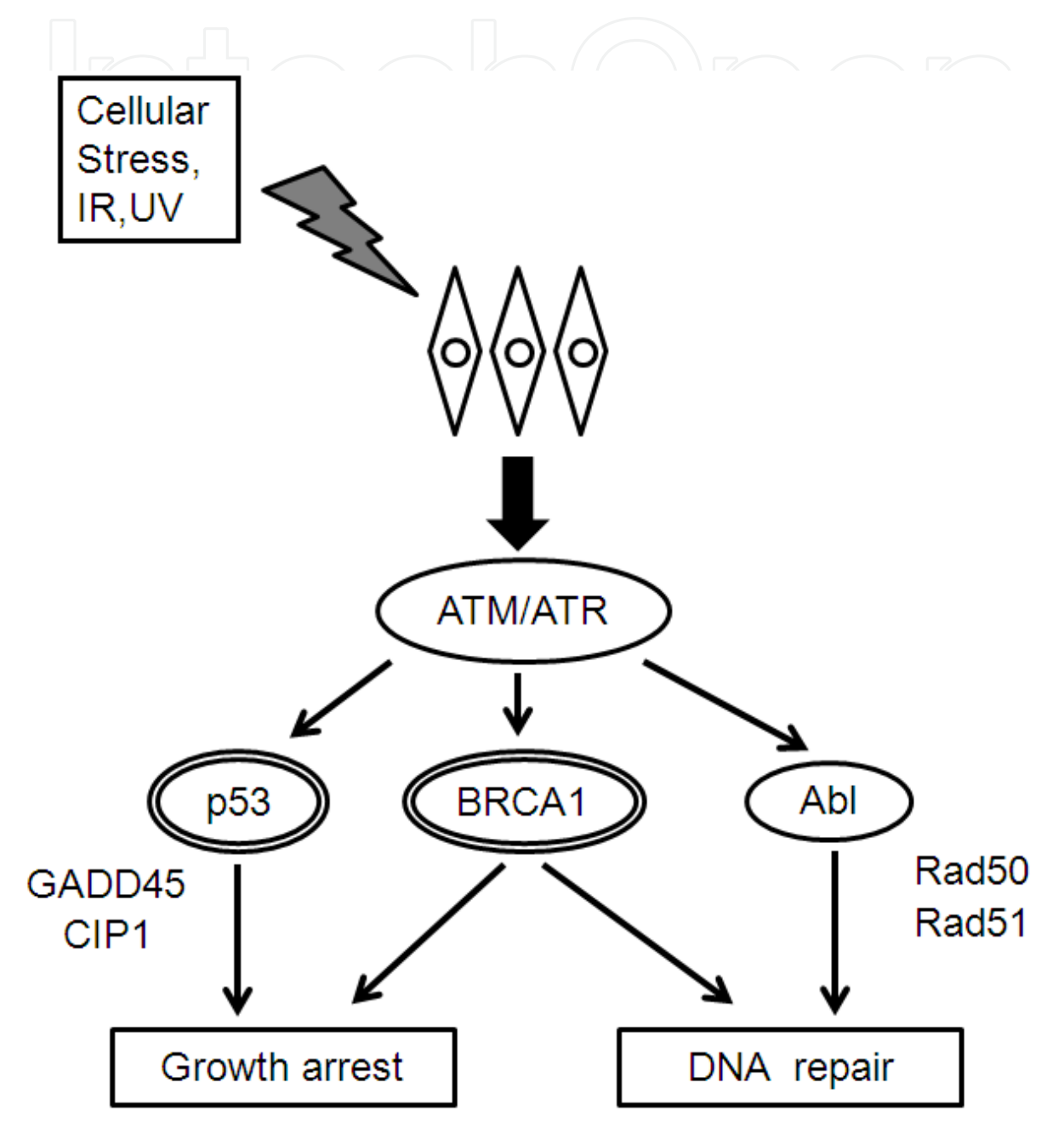


Figure 1. Schematic representation of the DNA repair and Growth arrest signaling pathways. Examples of the molecule known to act on the regulatory pathways are shown.

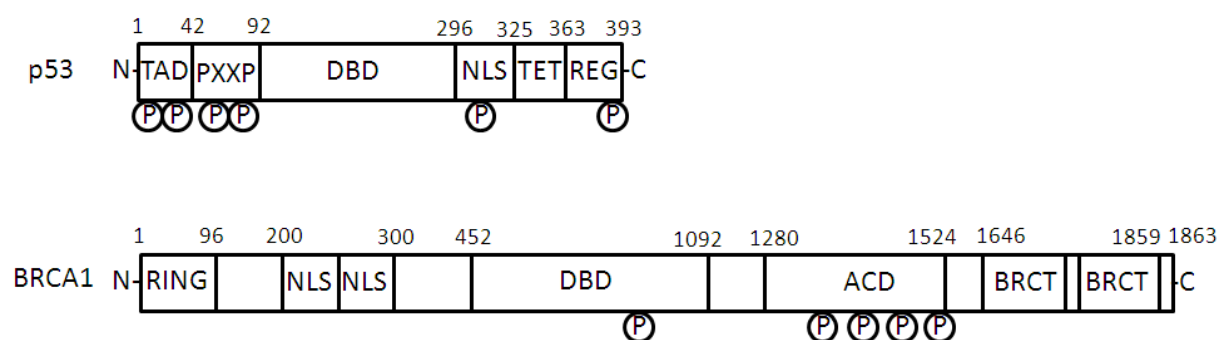


Figure 2. Schematic diagram indicating the domain structures of the p53 and BRCA1 proteins. The functionally important sites including the sites of protein phosphorylation are also shown.

2. Function and involvement of p53 in DNA repair pathway

The p53 is a transcription factor that regulates a number of genes and protects against genomic instability. It is inactive under normal physiological conditions and activated in response to various types of cellular stresses including DNA damage. Under the stress conditions, p53 functions to block cell cycle progression [10], and failure of the DNA repair mechanisms leads to p53 mediated induction of apoptotic cell death programs. The p53 protein is also induced and activated in the nucleus by a stress such as hypoxia and oxidative stress. In addition, p53 undergoes post-translational modifications such as acetylation of lysines, nitration of tyrosines, phosphorylation of serine/threonine residues in response to those stresses [11]. Activated p53 protein regulates its downstream genes and subsequently inhibits malignant transformation of normal cells. Because p53 plays an important role in the transcriptional regulation of genes encoding proteins involved in DNA repair and programmed cell death, the modification of p53 protein appears to be a pivotal determinant of cells fate in some conditions.

The p53 protein is involved in a lot of signaling pathways of cell growth regulation, and multiple mechanisms have been revealed to accomplish the regulation of p53 activity, which determines the selectivity of p53 for specific transcriptional targets, resulting in control of the p53 activity. A large number of molecules capable of activating p53 have been developed. Studies have documented the importance of Mdm2 in the control of the p53 activity [12]. MdmX is also recognized as the p53 negative regulators [13]. A p14 ARF controls the level of p53 by inhibiting the p53-specific ubiquitin ligase MDM2 [14]. The MdmX has been identified as a highly homologous gene that is closely related to Mdm2. Although MdmX possesses a p53 binding domain at its N-terminus, the MdmX does not have ubiquitin ligase activity like Mdm2. The 53BP1 protein also has a role in the cellular response to DNA damage. Convincing evidence exists for the 53BP1 affecting the outcome of DNA double strand break repair [15, 16]. Among a number of transcriptional targets of the p53, the p21WAF1 has been shown to play an important role in both p53-dependent and independent pathways [17]. The p21 WAF1 inhibits cell cycle progression through interaction with the cyclin and CDK complexes. CLCA2 has been reported as a p53 target gene that regulates the p53 induced apoptotic pathways. In addition, CLCA2 has been

shown to be down-regulated in breast cancer tissues [18]. ABL1 includes nuclear localization signals and a DNA binding domain through which it mediates DNA damage repair functions. Several ABL targets including the p53 are primary regulators for the DNA damage induced apoptosis [19, 20]. Ciz1 is an estrogen-responsive gene (ER), whose product co-regulates ER by enhancing its transactivation activity. The Ciz1 protein induces hypersensitivity of breast cancer cells to estrogen and induces the expression of ER target gene such as cyclin D1 [21]. Moreover, Ciz1 promotes the proliferation, anchorage independent growth of breast cancer cells. The Ciz1 protein also interacts with a novel protein named PDRG1, which is regulated by the p53 and DNA damage [22].

The gene of the p53 is frequently mutated in multiple cancer tissues, suggesting that p53 plays a critical role in preventing cancers. Studies have shown that p53 is mutated or deleted in nearly half of all human cancers. During neoplastic progression, the p53 is often mutated and fails to perform its normal functions. Mutant p53 can be classified as a loss of function or a gain of function proteins depending on the type of mutation. The p53 activation by something cellular regulator including a gain of function-mutation may lead to regression of an early neoplastic lesion, and therefore may be important in developing cancer chemoprevention.

3. Function and involvement of BRCA1 in DNA repair pathway

Mutations in the tumor suppressor gene BRCA1 confer an increased risk for the development of breast and ovarian cancers [23]. BRCA1 hereditary breast cancer is a type of cancer with defects in a DNA repair pathway. Actually, mutation of a single allele of the cancer susceptibility gene BRCA1 is associated with increased genomic instability in human breast epithelial cells [24], which accelerates the mutation rate of other critical genes. Several functions of BRCA1 may contribute to its tumor suppressor activity including roles in the DNA repair. Although BRCA1 gene mutations are rare in sporadic breast and/or ovarian cancers, BRCA1 protein expression is frequently reduced in the sporadic cases.

The BRCA1 has the important role in concert with BRCA2, Rad50 and Rad51 [25], in order to activate the checkpoints. For example, BRCA1 is colocalized with Rad51, a DNA recombinase related to the bacterial RecA protein. The BRCA1 protein becomes hyperphosphorylated after exposure to the DNA damaging agents, and the function of BRCA1 seems to be regulated by the phosphorylation in response to DNA damage. Pharmacological inhibition of poly-ADP-ribose polymerase induces cell death in tumors with mutations in certain DNA repair pathways, when combined with DNA damaging chemotherapies. Then, poly-ADP-ribose polymerase inhibitors have been investigated for the treatment of patients with BRCA 1 mutation, as a strategy to potentiate the DNA damaging effects of chemotherapy and irradiation [26, 27].

The BRCA1 plays an important role in maintaining genomic integrity by protecting cells from double-strand breaks that arise after DNA damage. The BRCA1 cDNA encodes for 1863 amino acids protein with an amino terminal zinc ring finger motif and two putative

nuclear localization signals (**Figure 2**). The amino-terminal domain possesses E3 ubiquitin ligase activity [28] and the carboxyl-terminal domain is involved in binding to specific phospho-proteins. The role of BRCA1 in cell cycle control has been understood by its ability to interact with various cyclins and cyclin-dependent kinases. The BRCA1 activates the CDK inhibitor p21 and the p53 tumor suppressor protein, which regulates several genes that control cell cycle checkpoints. BRCA1 also has binding domains for Rb, Rad50 and Rad51 [29, 30]. They may also be involved in DNA double strand break repair. Previous studies have suggested that the BRCA1 pathway dysfunction may also provide an opportunity for therapeutic intervention.

4. DNA repair and cancer therapy

DNA damaging strategies are frequently used as nonsurgical therapies against cancers. Among them, methylating agents such as cisplatin and ionizing radiation are important. DNA double strand breaks are induced following the exposure to the methylating agents [31]. Those also activate the DNA damage checkpoints, which induce cell cycle arrest in order to repair the DNA damage. However, down-regulation of DNA repair mechanism promotes genetic instability, which can lead to carcinogenesis. When defects in certain DNA repair molecules are present in immune system, for example, lymphocyte development can be compromised and the patients can consequently develop primary immune-deficiencies. Those patients often have a predisposition for cancer development. An additional consequence of defective DNA repair is cellular hypersensitivity to DNA damaging agents [32]. In another words, DNA damaging agents work well in cells with DNA repair defects. Mutations in BRCA1, for example, make cancer cells highly susceptible to inhibitors of a DNA repair pathway such as poly-ADP-ribose polymerase [33]. Inhibition of DNA repair pathway also seems to block the mechanisms that are required for survival in the presence of oncogenic mutations. As the consequence, selective elimination of the mutation bearing cells occurs, which can upregulate the DNA repair system. Epigenetic mechanisms such as histone modifications and DNA methylation have been evaluated with a view for enhancing the cancer therapy via the regulation of the expression of genes involved in DNA repair [34].

Treatment of cancers with DNA damaging therapy causes cytotoxicity through induction of high levels of the DNA damage. Cancer cells also respond to DNA damage by activation of the DNA repair and may counteract chemo and radiation efficacy. Actually, DNA repair have been shown to influence radiosensitivity, and the activation of DNA repair of cancer cells might be one of the most important factors in the therapeutical resistance. Inactivation of ATM give rise to cell cycle defects in response to irradiation and radiosensitise cancer cells [35]. In this way, Zebularine and 5-aza-2'-deoxycytidine are employed as radiosensitizing agents [36, 37]. Histone deacetylase inhibitors such as LBH589 and MS-275 have been shown to enhance radiosensitivity through the similar mechanisms [38]. Several histone deacetylase inhibitors exert direct cytotoxic effects and sensitize cancer cells to radiotherapy. For example, trichostatin A, which is the potent histone deacetylase inhibitor enhances radiosensitivity in a variety of human cancers [39]. A previous study has

demonstrated that a histone deacetylase inhibitor downregulate the expression of Rad51, which participate in the DNA repair pathway. The marine product, psammaplin A, has been shown to have potent cytotoxicity against several cancer cells. As psammaplin A has been shown to exhibit histone deacetylase inhibitory activity, this may be a promising radiosensitizing agent [40]. Actually, the psammaplin A has the potential to increase radiosensitivity in lung cancer A549 and glioblastoma U373MG cells. Thus, it has been found that a variety of histone deacetylase inhibitors synergistically enhance the growth inhibition and apoptosis of DNA damaging drugs. As numerous parameters may influence cancer therapeutical sensitivity, the impairment of DNA repair may be one of the most crucial mechanisms underlying enhanced the therapeutical responses. So, detection of DNA damage and repair pathways is important component of the intrinsic therapy sensitivity (Figure 3).

Platinum compounds such as cisplatin and carboplatin are one of the most widely used and effective chemotherapeutic agents for several cancers including cerebellar tumor and medulloblastoma [41]. However, cancer cells often develop resistance to those genotoxic drugs. Improvements of the effectiveness to cancers are urgently needed. Some cell lines develop acute resistance to cisplatin in the presence of estrogen receptor antagonist. In the presence of it, cisplatin treated medulloblastoma cells show recruitment of Rad51 to the sites of damaged DNA lesions, and increase DNA repair activity. BRCA1 is required for subnuclear assembly of the Rad51 and survival following treatment with the cisplatin [42]. DNA damage in MCF7 cells in which estrogen receptor is activated, lead to the inhibition of cell cycle checkpoint, which results in less effective DNA repair [43]. DNA damage in the cancer cells in which estrogen receptor is inhibited, result in better DNA repair and improved cell survival, which attenuated cytotoxic action of cisplatin.

Proper intake of dietary nutrients including zinc has been considered crucial for preventing the initiation of events leading to the development of cancer. The zinc is an essential element that is integral to some transcription factors which regulate key cellular functions such as the response to oxidative stress and DNA damage repair. Zinc is involved in stabilization and activation of the p53 that appears to be an important component of the apoptotic process [44]. Thus, zinc provides an effective dietary chemopreventive approach to disease in a cancer, and zinc could be effective in the treatment of several cancers. However, it needs further exploration to investigate the genetic and epigenetic pathways of the effects by the zinc. There is interest in mechanisms of acquired resistance to epidermal growth factor receptor (EGFR) inhibitors that are being used in the treatment of a variety of cancers [45]. Acquired resistance to EGFR inhibitors is associated with the loss of p53 and cross resistance to irradiation. The p53 may enhance sensitivity to irradiation via induction of DNA damage repair at this point. The cytotoxic agents target stabilization of p53 through DNA damage. Thus, p53 represents an attractive target for therapeutic design and development of anticancer agents. Restoration of hypoxia induced p53-mediated signaling may well be effective in the targeting of hypoxic cells [46]. The DNA damage response is also induced in cells by the hypoxia.

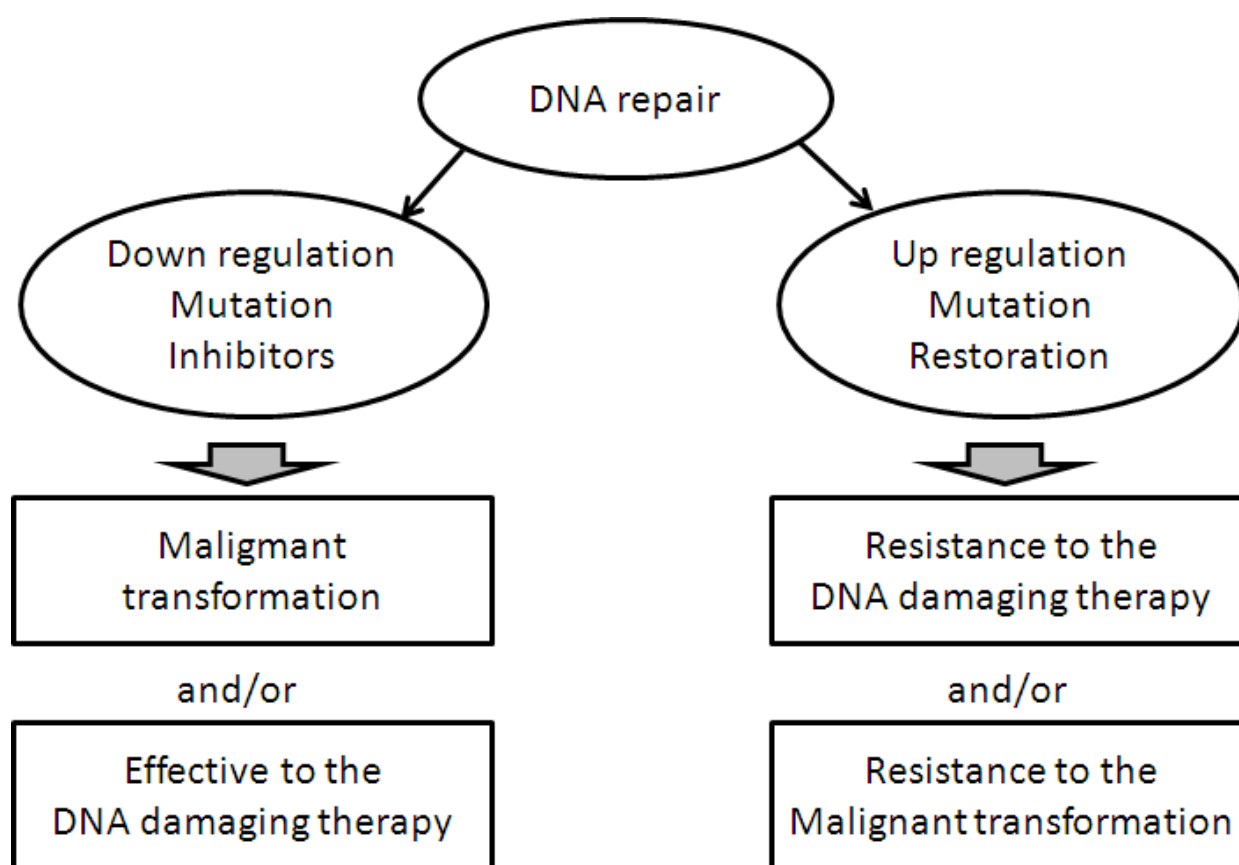


Figure 3. Implication of DNA repair modulations in cancer. DNA repair downregulation can contribute to genomic instability, which promotes malignant transformation of cells, and leads to cellular sensitivity to DNA damaging therapy. DNA repair upregulation can contribute to genomic stability, which lead to acquired resistance to the DNA damaging therapy.

5. Perspective

It has been paid more attention to the DNA repair as a therapeutic target, because DNA repair enzymes regulation and specific cytotoxic cancer therapy may be possible via the mechanism based on the appropriate DNA damaging approaches (**Figure 4**). The cancer cell genome is aberrant as a consequence of incomplete DNA repair. As many anticancer drugs further reduce the integrity of DNA, they may be able to cause more mutations and another cancer, if the lesions are not repaired. However, cancer cells, in which its DNA repair is down-regulated, have been shown to exhibit increased sensitivity to DNA damaging chemotherapy. A new therapeutic approach will be possibly developed, in which radiation therapy or cytotoxic anticancer agents are employed in conjunction with the DNA repair modulators. For example, cells exposing to hypoxia are sensitive to inhibition of components of the DNA damage response. The DNA damage response induced by hypoxia is distinct from the classical pathways induced by the DNA damaging agents due to the coincident repression of DNA repair in hypoxic conditions. The principle aims of the hypoxia induced DNA damage response seem to be the induction of p53 dependent apoptosis. Such combinations can cause severe genomic instability in cancer cells resulting

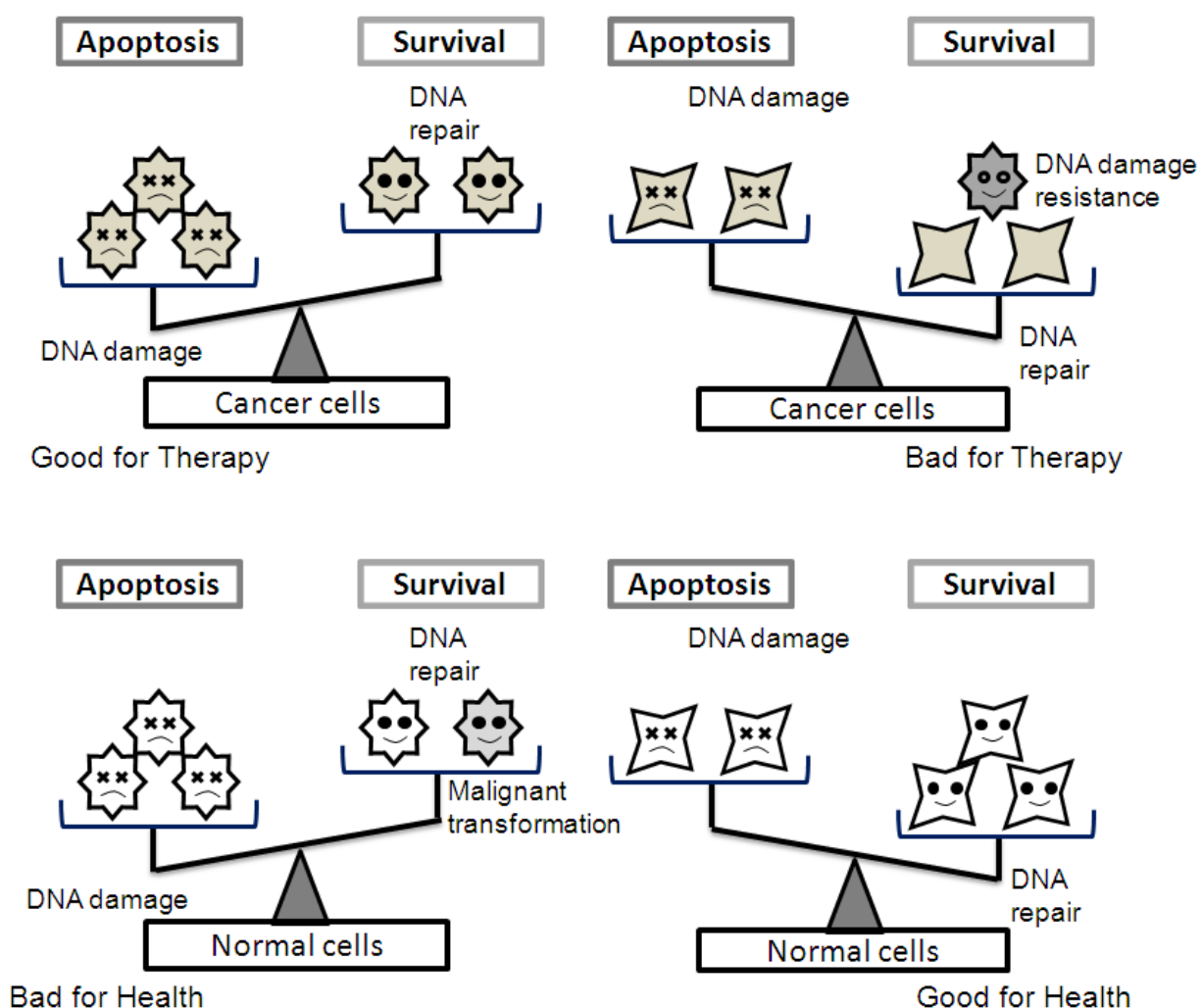


Figure 4. Survival or Apoptosis, that's the problem in cancer therapy and for individual health. The determination either survival or apoptosis is due to the balance between DNA damage and the DNA repair levels in cells.

in apoptotic cancer cell death. Tumor recurrence frequently occurs after genome damaging therapy, but the characteristics and the behavior of resistant cancer cells remain unknown. Recently, it has been reported that the peri-necrotic tumor cells after radiation therapy acquire hypoxia-inducible factor 1 (HIF-1) activity after surviving radiation, which triggers their translocation towards tumor blood vessels. So, the HIF-1 inhibitors suppress the incidence of post-irradiation tumor recurrence [47].

Understanding of the cellular aberrations of cancer cells has allowed the development of therapies to target biological pathways. Active inhibition of DNA repair enzyme in a tumor can lead to genomic instability and cell death by exploiting the paradigm of synthetic lethality, which potentiates anti-neoplastic effects of DNA damaging therapy including radiation. Several studies have evaluated the role of DNA repair enzyme inhibitors for treatment of cancer [48, 49]. In conclusion, the combination of DNA damaging agent and DNA repair enzyme inhibitor results in beneficial improved anticancer efficacy. However,

side effects of the blocking of DNA repair system on the normal cell may overcome their benefit action. So it is important to precisely investigate the effects in both the target and normal cells. Optimizing treatment according to tumor status for DNA-repair biomarkers such as BRCA1 could predict response to DNA toxic cancer therapies and might improve the response of tumors to the therapies. Variation in DNA repair genes may also be informative. Further investigations will be required to identify other additional mechanisms associated with the therapeutic sensitivity and other epigenetic drugs such as the histone deacetylase inhibitors. Investigations are warranted to determine whether alterations in the methylation patterns of set of genes involved in DNA repair might be modulated by the inhibitors. Also, future studies should be conducted to determine whether the combination of DNA damaging agents and DNA repair modulator has potential for the treatment against cancer.

Competing interests statement

The authors declare that they have no competing financial interests.

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Acknowledgement

This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology in Japan and Nara Women's University Intramural Grant for Project Research.

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