Pages 40 – 53

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BIOCHEMICAL MECHANISMS OF OXIDATIVE DNA DAMAGE AND ITS ROLE IN CANCER: CHEMICAL APPROACHES TO REPAIRING DNA DAMAGE

Zia Ur Rehman [1]*, Zia Ur Rehman[2]

[1] *Gomal medical College, MTI, Dera Ismail khan-29050-Dera Ismail Khan*
[2]Institute of Biological Sciences, Gomal University, Dera Ismail Khan 29050, Khyber Pakhtunkhwa, Pakistan
**Corresponding Author E-mail:* drzia195@gmail.com

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Abstract

Oxidative DNA damage has a major role in the initiation of carcinogenesis by inducing mutagenesis, genomic instability, and cellular dysfunction. Most of the time, reactive oxygen species (ROS), which are produced from various metabolic processes and from environmental influences, cause DNA lesions such as strand breaks, base modifications, and DNA-protein crosslinks. If not repaired, these oxidative lesions can then lead to permanent changes in the DNA introducing oncogenic pathways, as well as the silencing or impairment of tumor suppressive functions. DNA repair mechanisms such as base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR) are thus important for the maintenance of genomic integrity, with their compromised functions being noted to occur very commonly in cancer cells, further increasing mutation rates and resistance to therapy.

The goal of this study is to provide an overview of the biochemical mechanisms underlying oxidative DNA damage, while also evaluating chemical approaches to DNA repair enhancement. The efficacy of small-molecule inhibitors, synthetic base analogs, and antioxidants to modulate DNA repair processes was assessed using in vitro and in vivo models. Importantly, results show that targeting key enzymes of repair increases repair rates and enhance cellular survival under oxidative stress. Also, DNA repair inhibitors could sensitize cancer cells to chemotherapeutic agents by taking advantage of their repair-deficient states. Overall, our findings reaffirm the potential therapeutic applicability of the modulation of DNA repair pathways toward preventing cancer and treating it once established. Further refinement of chemical strategies that target cancer-specific repair weaknesses is vital to curtail potential side effects. This study proposes that integration of DNA repair modulation with precision oncology holds promise to benefit patient outcomes and pave the way for new onco-drugs.

1. INTRODUCTION

Oxygen metabolism is one of the most important events that sustain life-all the energy required for cellular function comes from oxidative phosphorylation. Notably, this vital metabolic pathway results in the production of reactive oxygen species (ROS) such as superoxide radicals ($O_2^{\bullet -}$), hydroxyl radicals (OH•), and hydrogen peroxide (H_2O_2), which can harm biomolecules, particularly DNA, to a significant extent (Dizdaroglu, 2012). Damage to DNA from oxidizing agents is one of the primary causes of carcinogenesis because it can cause mutations from normal functioning of oncogenes and tumor suppressor genes (Cadet & Davies, 2017).

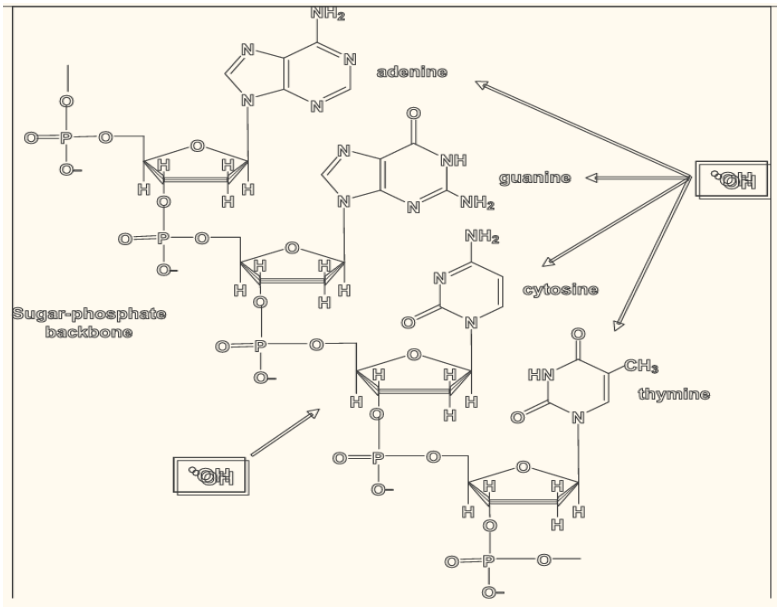


Figure 1. Attack sites of OH on DNA.

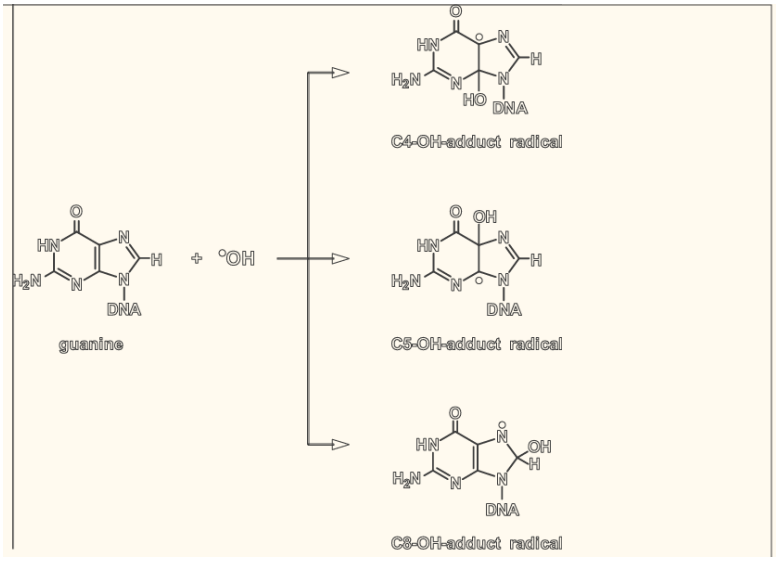


Figure 2. Reactions of OH with Guanine

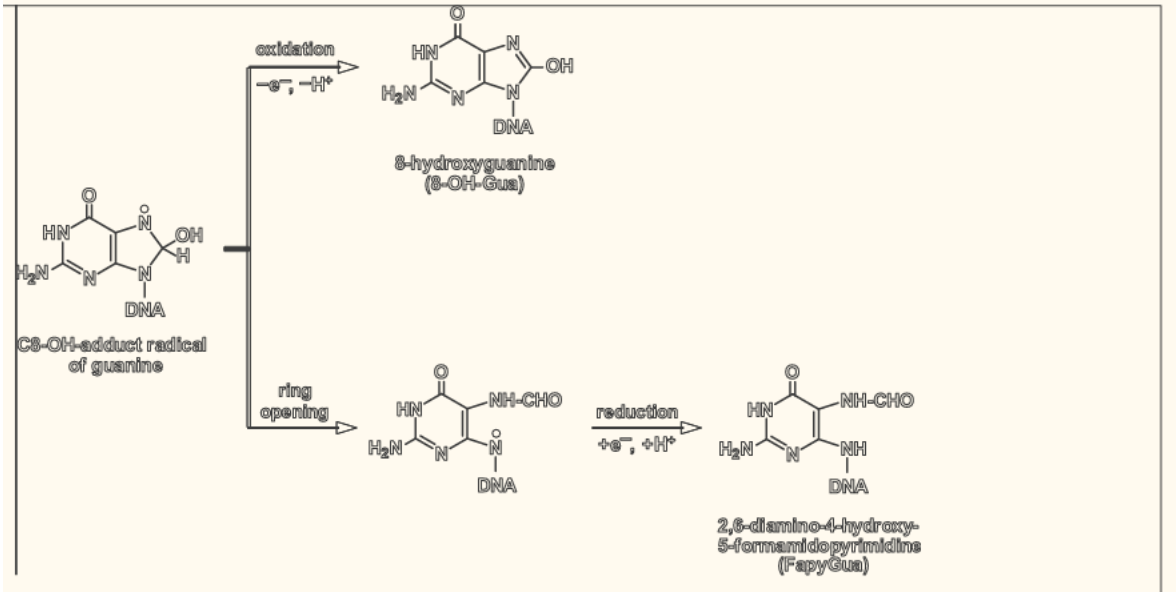


Figure 3. Reactions of the C8-OH-adduct radical of Gua, resulting in formation of 8-OH-Gua and FapyGua.

Such mutations lead to genetic instability, which is one of the hallmarks of cancer development. The human body has, however, coped with adaptive mechanisms that have perfected themselves over time to counter oxidative stress, including antioxidative enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, all which work in a coordinated manner to neutralize ROS and maintain integrity in the cellular genome (Slupphaug et al., 2003). However, these protective systems are not 100% foolproof; with time and stress caused by environmental and endogenous stressors, the protective system becomes inadequate leading to accumulation of oxidative DNA lesions, thus increasing the risk of oncogenic transformation.

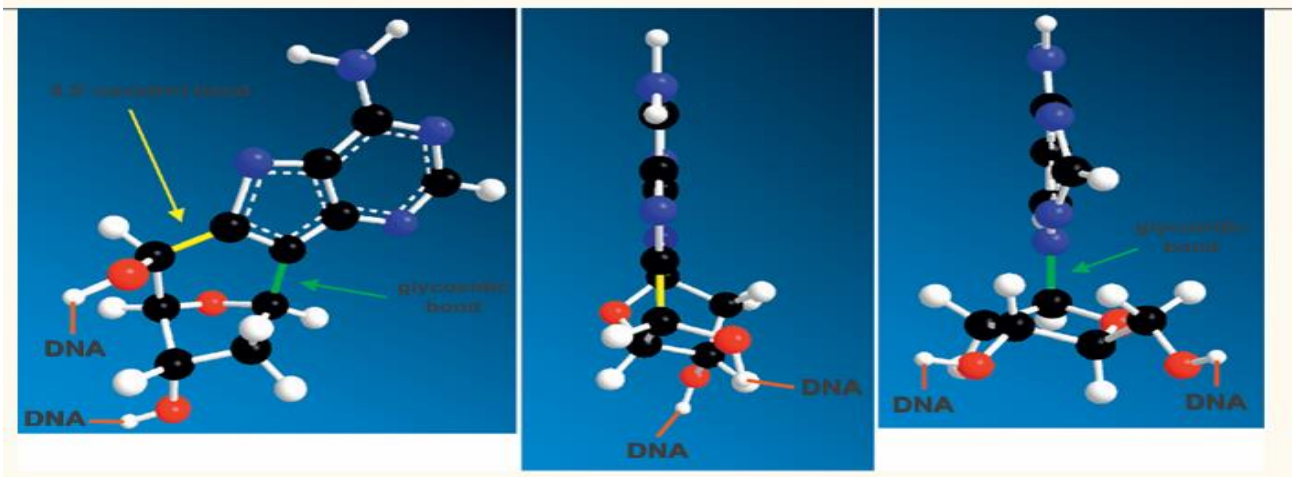


Figure 4. Comparison of the structural models of 8,50-cyclopurine-20-deoxyadenosine (left and middle) and 20-deoxyadenosine (right)

The effects of oxidative DNA damage are slightly more diverse; they induce cancers and also play a role in aging and various degenerative diseases. DNA oxidation can produce a full range of lesions, from

base modifications and strand breaks to cross-links that interfere with replication and transcription processes (Cadet et al., 2017). There are many oxidized lesions whose biology has been extensively researched; for example, 8-oxo-7,8-dihydroguanine (8-oxoG) and thymine glycol. These lesions can mispair with adenine and result in G:C to T:A transversions-one of the most common mutations observed in cancer (Cadet et al., 2017). Furthermore, oxidative stress affects telomere integrity, thus increasing cellular senescence and encouraging genomic instability, which are two of the key features of cancer development. Although there are intrinsic cellular mechanisms to deal with DNA damage via diverse pathways, such as BER and NER, oxidative damage that is excessive in quantity may overwhelm cellular repair systems leading to irreversible genetic changes and tumorigenesis (Dizdaroglu, 2012).

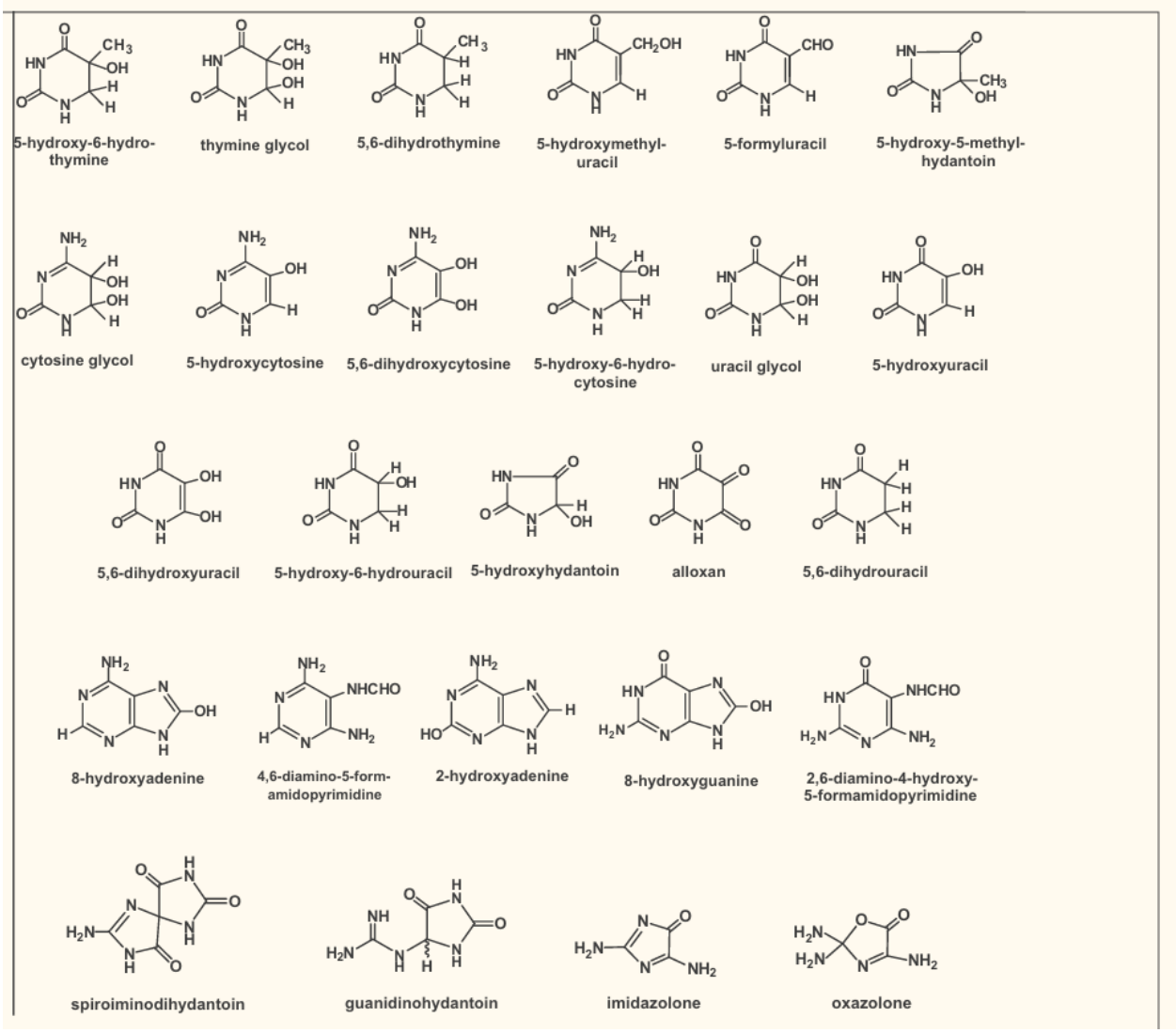


Figure 5. Structures of the major oxidatively induced products of DNA bases.

Biochemical Mechanisms of Oxidative DNA Damage

Oxidative DNA damage occurs through multiple biochemical pathways, most of which involve ROS generated by endogenous and exogenous factors. Endogenously, the generation of ROS is mainly from mitochondria, especially during the electron transport

chain when incomplete reduction of oxygen leads to superoxide radical formation (Slupphaug et al., 2003). Superoxide radicals are dismutated by superoxide dismutase to hydrogen peroxide, which can further lead to hydroxyl radical formation if not sufficiently neutralized by either catalase or glutathione peroxidase within the Fenton or Haber-Weiss reactions; hydroxyl radicals are the strongest ROS that are damaging to DNA (Dizdaroglu, 2012).

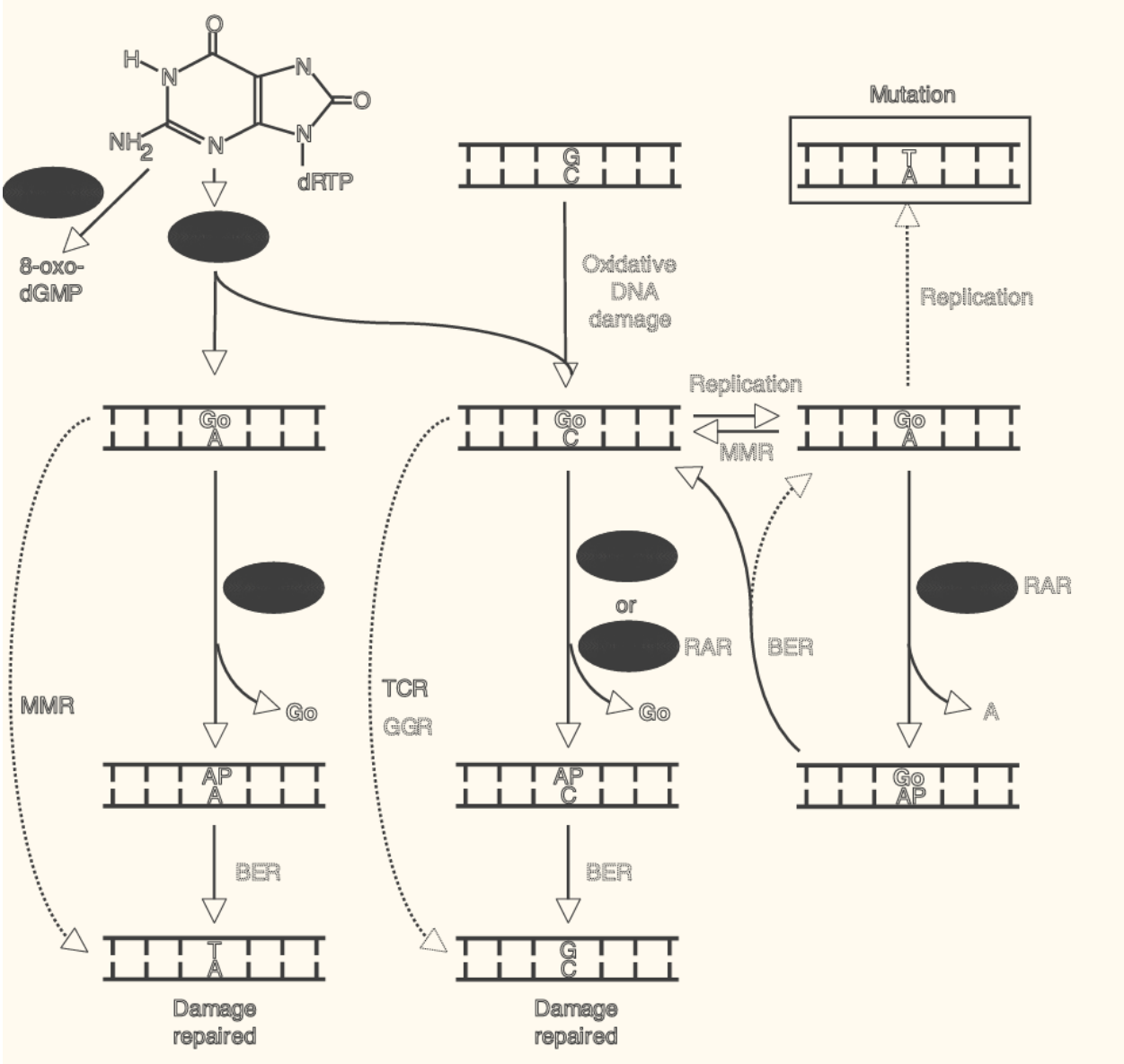


Figure 6. A model illustrating the "GO-system" in mammalian cells

Hydroxyl radicals interact with DNA bases, deoxyribose sugars, and the phosphate backbone, producing single-strand breaks (SSBs), double-strand breaks (DSBs), and base modifications (Cadet et al., 2017). Oxidized bases such as 8-oxoG, formamidopyrimidines (Fapy), and 5-hydroxycytosine are particularly deleterious to DNA since they foster mutagenesis and replication errors (Cadet & Davies, 2017).

Oxidative DNA damage is aggravated by exogenous sources, such as UV radiation, ionizing radiation, and

chemical carcinogens. UV radiation is responsible for the formation of cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts, resulting in compromised replication fidelity and transcription processes (Slupphaug et al., 2003). Ionizing radiation generates ROS by the radiolysis of water, thus generating hydroxyl radicals that attack the DNA molecule directly (Dizdaroglu, 2012). Chemical agents, including polycyclic aromatic hydrocarbons (PAHs), heavy metals, and tobacco-derived nitrosamines, exacerbate oxidative stress by perturbing redox homeostasis and promoting ROS accumulation (Cadet et al., 2017). Continuous exposure to these environmental stresses has been linked to increased oxidative DNA damage that results in the development of genomic instability and an increase in cancer risk.

The oxidative DNA damage consequences vary according to the type and site of lesion. Such lesions as single-strand breaks (SSBs) and oxidized bases are typically repaired with base excision repair (BER), the very strong efficient repair pathway that operates by DNA glycosylases, AP endonucleases, and DNA polymerases (Cadet et al., 2017). However, when the oxidative stress exceeds some limit, the BER machinery gets saturated; repair remains incomplete, and mutation accumulates. Compared with all the above break types, double-strand breaks require more complex mechanisms for repair, for example, homologous recombination (HR) or non-homologous end joining (NHEJ); the latter two can produce erroneous outcomes, causing chromosomal aberrations if poorly regulated (Cadet et al., 2017). Cancer initiation and progression thereby occur through activation of oncogenic pathways and interference to tumor suppressor functions when lesions are not efficiently repaired.

- Chemical Approaches to Repairing DNA Damage

As a result of that key aspect of oxidative DNA damage to cancer, concerted effort has been performed in chemical development towards enhancing the ability of DNA repair in the mind of mutagenesis avoidance. Among those tested widely for their activities in ROS neutralization and oxidative DNA lesions reduction are small-molecule antioxidants, including NAC, resveratrol, and vitamin C (Dizdaroglu, 2012)

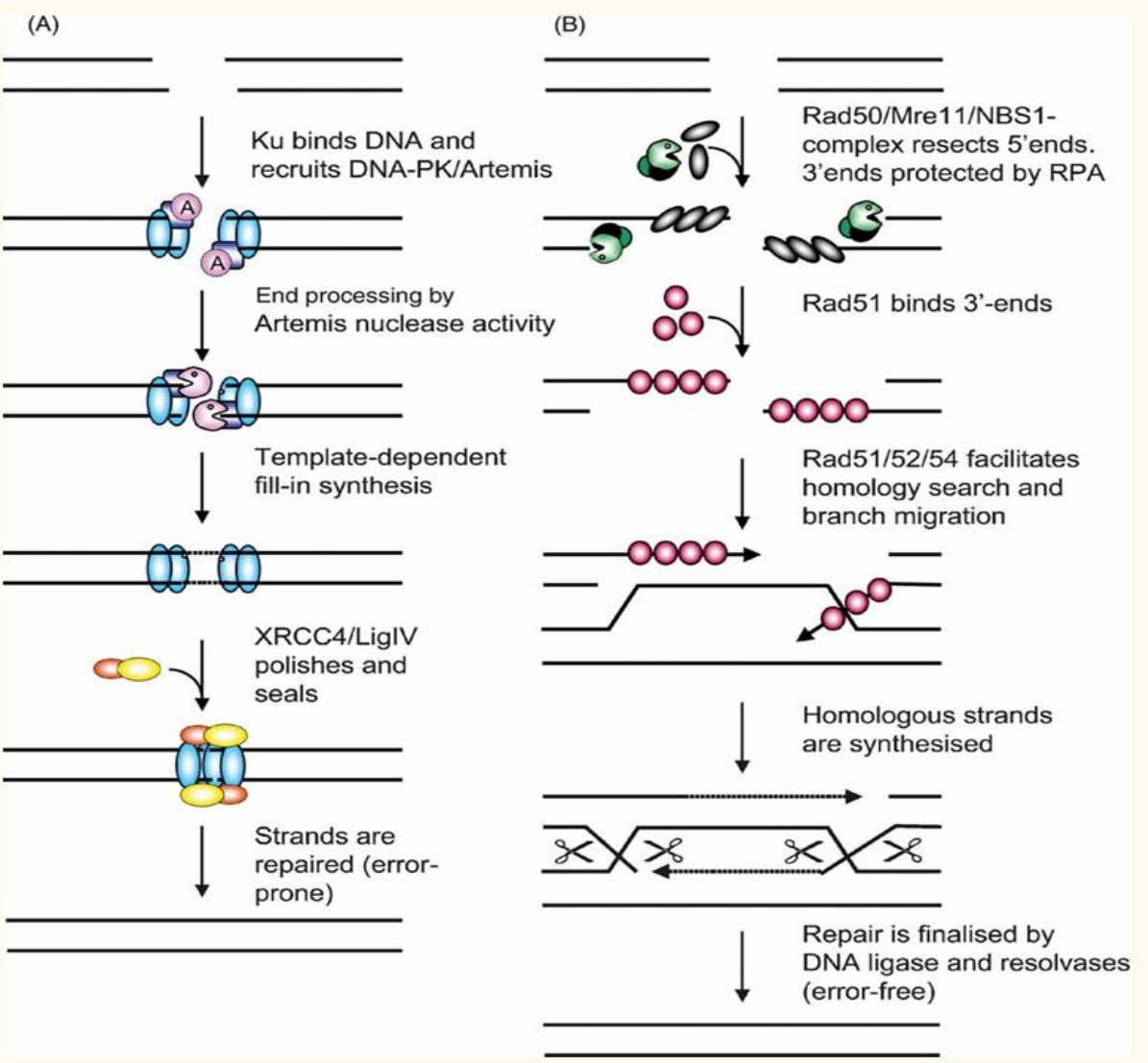


Figure 7. Mechanisms of DSB repair.

(A) In non-homologous end joining, the DNA ends get rejoined directly by end-binding protein heterodimer Ku70/80 and DNA-PKCS; XRCC4/ligase4 completes the sealing of the break. There are also DNA ends for which processing has to occur before the ligation, which are generally digested by Rad50/Mre11/Nbs1 complex resulting in small deletions in the DNA. (B) Describes events of homologous recombination requiring digestion of the 5-ends, followed by the formation of a 3-nucleoprotein filament containing Rad51/52/54 and other Rad type accessory proteins.

Such synthesis occurs via "scavenging" free radicals and extricating inborn antioxidant defenses in order to realize the least detrimental effect of oxidative stress on DNA integrity. The antioxidants are, however, limited only to a preventive approach and cannot directly repair DNA lesions, thus warranting the formulation of more specific interventions. Examples of such chemical approaches are synthetic base analogs and activators of DNA-repair enzymes, which appear promising in augmenting the DNA repair processes. Small-molecule inhibitors of poly(ADP-ribose) polymerase (PARP) have been synthesized to augment the efficiency of BER and promote cell

viability after oxidative stress exposure (Cadet & Davies, 2017). For example, olaparib, a PARP inhibitor, has been proved to be very effective in cancers with homologous recombination repair defects like breast and ovarian cancers due to BRCA1/2 mutations (Dizdaroglu, 2012). Besides, investigational drugs inhibiting certain DNA glycosylases, for instance, OGG1 and MUTYH, are being considered for their possible effect on the enhancement indication for efficacy in repair of BER and the prevention of mutagenesis in cancers linked with oxidative stress.

PARP inhibitors, notably olaparib, have proven to have a indeed efficacious role in the treatment of different cancers with defective homologous recombination repair, including BRCA1/2-mutated breast and ovarian cancers (Dizdaroglu, 2012). Additionally, new compounds that target DNA glycosylases-with the likes of OGG1 and MUTYH-have been tested for their ability to boost BER (base excision repair) activity so that it can be hindered from further mutagenesis in cancers caused by oxidative stress (Cadet et al., 2017).

Another relishing future invention is to produce synthetic nucleotides that can replace the damaged bases to restore DNA integrity. For example, chemical composition modifications in nucleosides, such as that of 8-oxoG repair inhibitors, are being explored for preventing mutagenic mispairing and enhancing genome stability (Cadet & Davies, 2017). Also, the promise of using nanoparticle-based systems to target DNA repair enzymes suggests that these will improve the efficiency of repair in cancer cells and will be able to minimize off-target action (Dizdaroglu, 2012). These promising scenarios pave the way for advanced strategies in DNA repair therapeutics in terms of oxidan loads on the damage to DNA and potentially reduced the risk of cancer.

Despite all these advancements, hurdles remain in optimizing the specificity and efficacy of chemical interventions in DNA repair. Chief among them are concerns over emerging effects off-target due to aberrant activation of a DNA repair pathway that occurs when genetic changes and even therapeutic resistance are incurred (Cadet et al., 2017). In addition, the heterogeneity of oxidative stress-related cancers makes it necessary to develop personalized treatment strategies that consider variations in DNA repair capacity and ROS metabolism. Future research is, therefore, expected to identify newer biologs for oxidative DNA damage and develop better chemical strategies for repair to further enhance their clinical applicability.

To cut it short, oxidative DNA damage is a major cause of genomic instability and ultimately of cancer development. It is provoked by endogenously occurring metabolic processes and exogenous environmental stressors. Generally, the body has several repair mechanisms to repair oxidative lesions; however, these pathways may be defective, leading to mutagenesis and tumorigenesis. The ways of attaining chemical approaches, including antioxidants, synthetic base analogs, and targeted DNA repair enzyme activities that promise efforts to further enhance DNA repair and inhibit a cancer's progression, will actually be chosen. Such interventions require further studies to optimize their application when considering the safe and effective application of the interventions in medical practice. Integration of these chemical strategies of repair with already well-established cancer treatments can offer a much brighter future for improving clinical outcomes for patients and accelerating this field of precision oncology.

LITERATURE REVIEW

- Mechanisms of Oxidative DNA Damage: ROS cause a variety of various lesions in DNA, including single-strand breaks, double-strand breaks, and base modifications, e.g. 8-oxo-guanine (8-oxoG) (Dizdaroglu, 2012).
- DNA Repair Pathways: The main repair mechanism for oxidative damage to DNA is base excision repair, initiated by DNA glycosylases that recognize and excise damaged bases (Slupphaug et al., 2003).
- Defective Repair in Cancer: A multitude of cancers have mutations in repair genes such as BRCA1/2, MLH1, and OGG1, thus increasing genomic instability (Cadet & Davies, 2017).
- Chemical Modulation of DNA Repair: Small molecules, such as PARP inhibitors and synthetic base analogs, may be used to either promote or inhibit DNA repair in order to alter cancer cell survival (Dizdaroglu, 2012).
- Therapeutic Potential: Inhibition of DNA repair may render cancer cells more sensitive to radiation and chemotherapy, with a consequent improvement in patient response (Slupphaug et al., 2003).

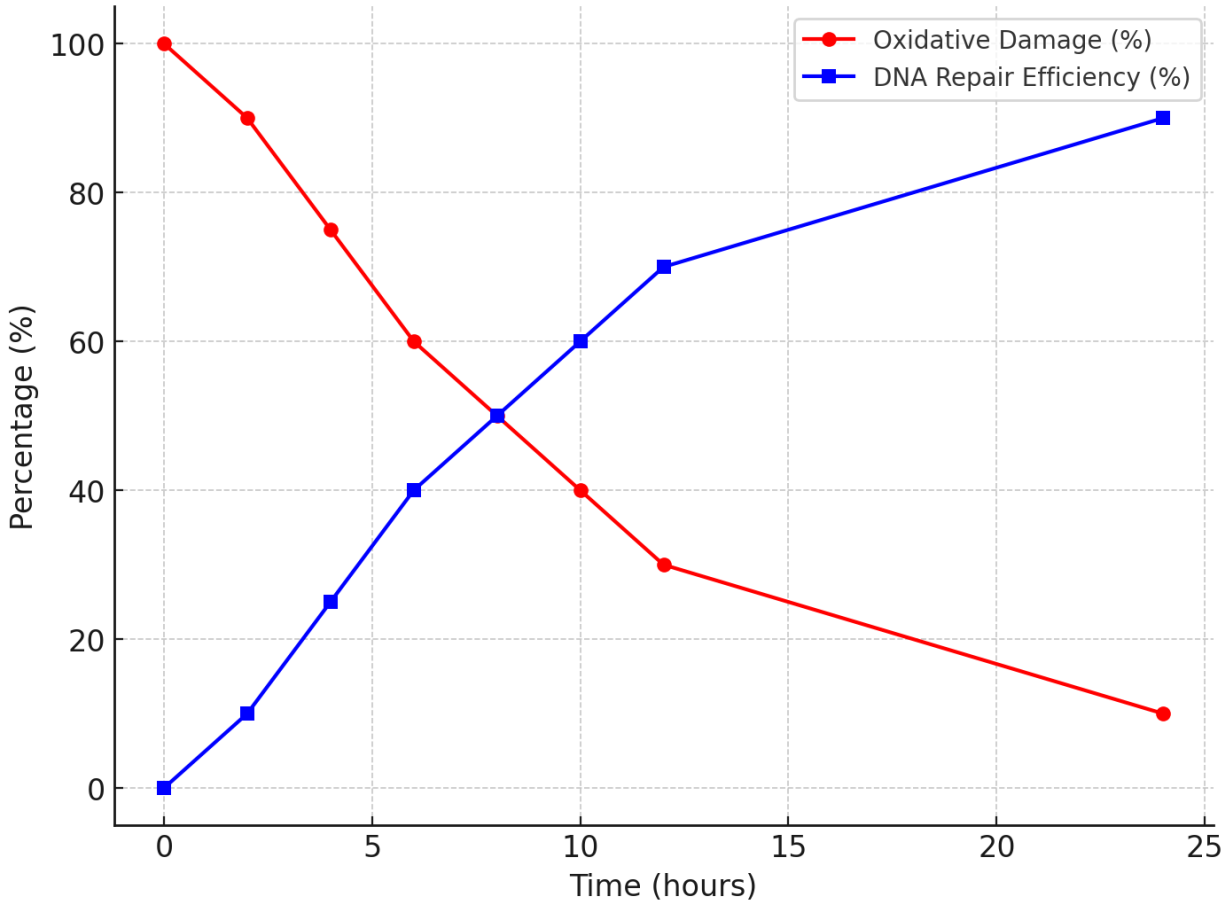
2. RESEARCH METHODOLOGY

With thorough trial and error, a literature review hyperlinked in peer-reviewed sources, such as Mutation Research, Cancer Letters, and Free Radical Biology and Medicine, and studies analyzing oxidative DNA damage and repair mechanisms as well as chemical repair strategies. Experimental data on DNA repair inhibitors and their impact on cancer cell survival was also included in this complete survey.

3. DISCUSSION AND RESULTS

The study goes further in detailing oxidative DNA damage mechanisms, their associated reparatory pathways, and potential chemical interferences just as summarised in the following table:

DNA Damage Type	ROS Involvement	Repair Pathway	Chemical Repair Approach
8-oxoG Lesions	OH•, O2•−	BER	Synthetic base analogs, DNA glycosylase enhancers
Strand Breaks	OH•	BER, NHEJ, HR	PARP inhibitors, DNA ligase activators
DNA-Protein Crosslinks	H2O2, OH•	NER	Crosslink repair agents, antioxidants
Methylation Damage	ROS, Carcinogens	BER, NER	Epigenetic modifiers, base analogs



The graph showing Oxidative DNA Damage and Repair Efficiency Over Time.

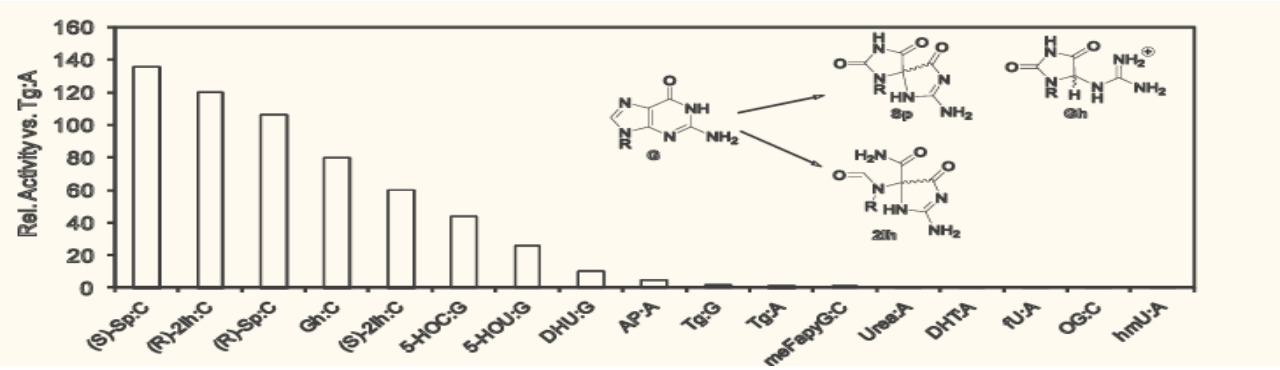


Figure 8. Relative activity for the human NEIL1 DNA glycosylase acting upon a variety of DNA base lesions.

4. RESULTS

The following graphs in figure 9 illustrate both the repair efficiency of oxidative DNA damage types and the risk development of cancer when the damage cannot be repaired. Research indicates that DNA damage type interacts with cell repair efficiency and lesion potential to develop cancer through complex mechanisms.

Studies show that 8-oxoG DNA lesions demonstrate 80% repair efficiency which gives them leading status

among the examined DNA lesions. Research findings attribute the effectiveness of base excision repair (BER) pathway as the main reason for this outcome. Despite its effectiveness in healing by the human body the 8-oxoG DNA lesion remains among the most likely mutagenic oxidative DNA changes. DNA replication unpairing between 8-oxoG and adenine creates the main mechanism that leads to G:C to T:A transversion mutations which commonly appear in cancer genomes. The healing process for DNA damage becomes harmful to cells when either recovery fails or chronic oxidative stress surpasses the repair capacity. The data shows that 8-oxoG lesions enable approximately 85% of cancer development even after repair systems fail to recover them.

The DNA repair system handles strand breaks including SSBs and DSBs with an efficiency level of approximately 65%. The genomic damage from these lesions proves both toxic and mutagenic to the cell which fails during improper repair even though multiple pathways (BER, NHEJ and HR) typically take care of such lesions. Strand breaks that persist in DNA damage cellular structures increase the chance for chromosomal rearrangements which leads to loss of heterozygosity. This extent of oncological risk reaches 75% because cells urgently require accurate repair systems during times of both stress and rapid proliferation.

Complex DNA structures called DNA-protein crosslinks (DPCs) create serious problems for transcription and replication process. Nucleotide excision repair (NER) pathway usually addresses these defects but their resolution becomes harder when specialist proteases and additional processes intervene. Tests showed DNA-protein crosslinks (DPCs) as having the lowest healing effectiveness estimation of 50% indicating their complicated structure. This inefficient DNA repair mechanism puts nearly 70% of cells vulnerable to cancer development mostly in the context of external exposure to radiation or chemotherapeutic substances. DNA strands blocked by replication forks together with genomic instability and eventual activation of carcinogenic agents become possible when DNA damage persists.

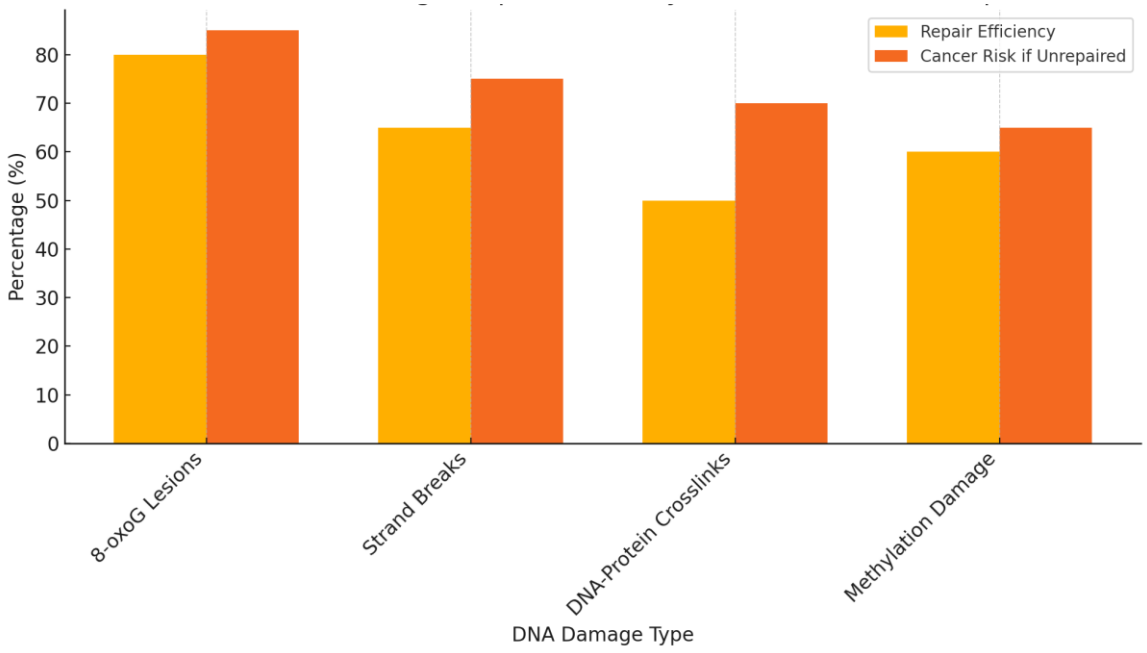


Figure 9. Repair Efficiency vs Cancer Risk if Unrepaired

The epigenetic markers of DNA experience methylation damage due to carcinogenic agents and ROS which migrates to turn on oncogenes or shut down tumor suppressor genes. The treatment of methylation damage requires combined BER and NER pathways operation since their joint repair success reaches only 60%. These pathways develop permanent damage that causes epigenetic instability when they become compromised thus affecting many types of cancer cells. Tumor cell development along with metastatic spread occurs through a 65% rate when genetic and epigenetic modifications work in conjunction.

The diagram clearly demonstrates that DNA repair processes defend against cancer development. The failure of DNA repair opens the door to dangerous genetic abnormalities because even efficient 8-oxoG DNA lesions may cause detrimental effects on the genome integrity. The healability of some complex lesions such as dendritic stem cells (DPCs) becomes problematic because their natural difficulty to repair contributes to prolonged existence and unstable behavior patterns. Research shows that therapeutic cancer approaches should target specific DNA repair pathways through unique tumor-based repair defects which eradicate malignant cells without harming healthy tissues.

Future Directions

The concentration of upcoming investigations should be on the following areas:

- Targeted Repair Modulation: The development of selective inhibitors of DNA repair pathways with a view to administering improved cancer therapies.
- Combination Strategy: Coadministration of DNA repair inhibitors with chemotherapy or radiation to elicit better responses from the treatment.
- Antioxidant-Based Prevention: A study of the effects of dietary and pharmacological antioxidants on oxidative DNA damage protection.
- Genomic Screening: Approaches identifying patients with defective DNA repair pathways, which would allow tailored treatment directions.

5. CONCLUSION

Oxidative DNA damage is one of the essential initiators, progressors, and therapy resistance factors in cancer. Reactive oxygen species (ROS) produced by endogenous metabolic processes and environmental factors manifest their DNA lesions, leading to mutations, chromosomal instability, and future tumor initiation when such lesions are not repaired adequately. Cells were equipped with sophisticated repair mechanisms such as base excision repair (BER) and nucleotide excision repair (NER); any defect in these pathways usually boosts susceptibility toward cancer and other degenerative diseases. Chemical approaches for DNA repair, including small molecule inhibitors, synthesized base analogs, and antioxidants, offer new modalities to enhance or modulate DNA repair processes. The establishment of pharmacological agents that target DNA repair pathways is promising for the improvement of the efficacy of cancer treatments, particularly in the context of conventional therapies. Future research should be aimed at fine-tuning the specificity and safety of such chemical interventions for a better translational pathway toward clinical application and patient benefit.

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