



Review Article

DNA technology as potential tool for neurological disorders

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ABSTRACT

Spontaneous decay or rupture of DNA caused by many of the factors leads to DNA damage such as mutation, single-strand breaks, double-strand breaks, mismatching, deamination, hydrolysis, and oxidation. DNA can be repaired by base excision repair, NER, direct excision, recombination, etc. This technique helps to treat many of the genetic disorders naturally or in the laboratories such as aging, carcinogenesis, diabetes, teratogenic complications, and cardiomyopathy. Various techniques were used such as polymerase chain reaction, different blottings, and gel electrophoresis. The future of the medical science on the basis of DNA repair to treat many neurological disorders will appear as a blockbuster in the upcoming few years. In the present paper authors have summarized various techniques to identify DNA damage, DNA repair and various applications of these techniques in treatment of different types of neurological disorders such as Huntington's disease, Alzheimer's disease and schizophrenia etc.

Keywords: Double-strand breaks, electrophoresis, polymerase chain reaction, single-strand breaks, teratogenicity

INTRODUCTION

DNA damage occurs due to change or mismatching of base pairs due to any endogenous (error during replication, mutation, apoptosis, senescence, free radicals and exogenous factors viz., exposure to [UV]- radiation, [IR]- radiation leads to DNA damage (Hájková *et al.*, 2017, Roriz and Moya, 2017, Alexandrov *et al.*, 2013).^[1-3] UV light induces two major damage adducts: cyclobutane pyrimidine dimers (CPDs) and pyrimidine(6-4) pyrimidone photoproducts (6-4PPs) (Freeman *et al.*, 1989).^[4] Which further leads to alterations in normal functions of DNA, which are so specific that can cause many somatic and germ cell dysfunctions. Studies of DNA damage are of special importance because DNA is the repository of genetic information.

DNA damage by different methods

Simple mutation: The development and function of an organism is in large part controlled by genes. Mutations can lead to changes in

the structure of an encoded protein or to a decrease or complete loss in its expression. Because a change in the DNA sequence affects all copies of the encoded protein, mutations can be particularly damaging to a cell or organism (Wallace *et al.*, 1988).^[5] Simplest mutations are switching of one base for another base. In transition one pyrimidine is substituted by another pyrimidine and purine with another purine. Chemicals in the environment pose myriad challenges to organisms, principally through toxicity or mutagenesis. Mutations are the result of changes in the DNA base sequence or the chemical addition of adducts onto the bases, which prevent correct DNA replication and/or transcription of the DNA into RNA (Ackerman and Horton, 2018).^[6]

Coordination

Heavy metal ions can form DNA-DNA intrastrand and interstrand cross-links through coordination. Cr (VI) complexes permeate cell membranes and are reduced to form Cr (III) complexes that can then coordinate with oxygen atoms of phosphate backbone of two adjacent nucleotides within one DNA strand or between two DNA strands, yielding Cr (III)-DNA intrastrand yielding interstrand cross-links (Brien *et al.*, 2002).^[7]

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Photoaddition

UV radiation leads to the formation of photoproducts (*e.g.*, CPD) by cycloaddition of the C5-C6 double bonds of adjacent pyrimidine bases. Six diastereomers are generated, depending on the position of pyrimidine moieties with respect to the cyclobutane ring (*cis/trans* stereochemistry) and on the relative orientation of the two C5-C6 bonds (*syn/anti* regiochemistry) (Cadet *et al.*, 2017).^[8] The *cis-syn* form is formed preferentially to the *trans-syn* diastereomers within double-stranded DNA.

The *trans-anti* and *trans-syn* photoproducts are only present within single-strand or denatured DNA (Ravanat *et al.*, 2001)^[9] [Figure 1].

Hydrolysis

AP sites are generated through spontaneous, chemically-induced, or enzyme-catalyzed hydrolysis of the *N*-glycosyl bond, losing genetic information. In mammalian cells, it has been estimated that approximately 12,000 purines are lost spontaneously per genome per cell generation (20 h) in the absence of any protective effects of chromatin packaging. It was subsequently shown that depyrimidination occurs with a rate about 100 times more slowly than depurination. Damaging chemicals, for example, free radicals and alkylating agents, promote the base release, mostly by generating base structures that destabilize the *N*-glycosyl linkage due to positively-charged leaving groups (Wilson and Barsky, 2001).^[10]

Oxidation

Oxidizing agents can produce 7,8-dihydro-8-oxo-2'-oxodeoxyguanosine (8-oxoG) lesions. 8-oxoG is a ubiquitous lesion arising from the oxidation of the C8 atom of G to form a hydroxyl group by free-radical intermediates of oxygen that are produced by chemical oxidation, ionizing radiation, or UV irradiation (Degan *et al.*, 1991; Fraga *et al.*, 1990).^[11,12] The enol (a lactim) at the C8-N7 position of G is converted to the more stable 8-oxoG lactam form.

Amination

Arylamines and *N*-acetyl arylamines are well-studied mutagens used as models and found in numerous occupational settings, tobacco smoke, and chemical dyes, leading toward the formation of adducts such as the models 2-aminofluorene (AF-dG) and *N*-acetyl-2-aminofluorene (AAF-dG) through amination of the C8 atom of guanine (*through* an initial N7 reaction, linking the amine group of the arylamine) (Vrtis *et al.*, 2013).^[13] 1-nitropyrene (1-NP) is the most abundant nitro-PAH, on a global basis. The active product of 1-NP (an ester of the reduction product hydroxylamine) forms a bulky *N*-[deoxyguanosine-8-yl]-1-aminopyrene adduct by reaction at the C8 atom of deoxyguanosine following an initial reaction at the N7 atom and rearrangement (Kirouac *et al.*, 2013).^[14]

Oxidative stress and DNA damage

Under pathological conditions of increased oxidative stress, it may cause damage to biomolecules (Barzilai and Yamamoto, 2004).^[15] Other biomolecules which may be affected by oxidative stress are nucleic acids. 8-oxoG, which is an oxidase analog of guanine, is the marker for this type of damage. The marker of oxidative DNA damage is detected not only peripherally but also in the brain (Szebeni *et al.*, 2017).^[16]

Even various CNS disorders are now linked to the DNA damage by oxidative stress, for example, depression (Black *et al.*, 2015).^[17]

1. Formation of pyrimidine dimers: This is very common in which formation of covalent bonds adjacent thymine bases. This leads to loss of base pairing with opposite stand.
2. Strand breaks: Sometimes, phosphodiester bonds break in one side of DNA helix. This is caused by various chemicals such as peroxides, radiations, and by enzymes like DNAases. This leads to break of DNA backbone. Single-strand breaks (SSBs) are more common than double-strand breaks (DBSs), which are most dangerous. Sometimes, X-rays, electronic beams, and other radiations may break the phosphodiester bond breaks in both strands which may not be directly opposite to each other. This leads to DBSs. Some sites on DNA are more susceptible to damage. These are called hot spots.

LINK BETWEEN APOPTOSIS AND DNA DAMAGE

Apoptosis (process of programmed cell death) is a prominent route of natural DNA damage. During the past few years, it was found that specific DNA lesion promotes apoptosis which leads to mutations, SSBs and DSBs (which is most dangerous) (Roos and Kaina *et al.*, 2006).^[18] Apoptosis induced by many genotoxins, which blockage the DNA replication, which leads to collapse of replication fork and cause DSBs, which further cause downstream lessons. DBS are detected by ataxia telangiectasia mutated (ATM) and ataxia telangiectasia Red3-related proteins, which signal downstream to CHK1, CHK2 (checkpoint kinases) and p53 causes, induction in transcriptional of proapoptotic factors such as FAS, PUMA, and BAX further leads to oncogene activation. This DNA damage triggers inhibition of RNA synthesis, which causes decline in the level of critical gene products like mitogen-activated protein kinase phosphatase (Britton *et al.*, 2014).^[19] This causes activation of JNK (Jun kinase), and finally, AP1, which stimulates death receptor activation, and this all scenario is done due to triggered signaling damage of p53 gene. This all would also guide us about therapeutic uses of anticancer agents which targets the DNA.

DIFFERENT KIND OF TECHNIQUES USED TO IDENTIFY DNA DAMAGE

1. Single cell gel electrophoresis or Cornet assay: In this, the cell is placed in an agarose suspension at a low melting point in alkaline conditions, and then, it is visible using any fluorescent stain to determine any DNA damage.
2. Alkaline elution: In this, the cell is lysed on membrane filters and SSBs are analyzed by measuring the rate of elution of single-strand DNA, the rate of elution denotes the length of DNA strand as well as the extent of damage.
3. Alkaline unwinding: First, the cell's DNA is unwound in the alkaline environment at SSB sites then sample passed from a column of hydroxylapatite then eluent is incubated with a fluorescent marker. Thus, we can read the number of breaks by estimating the number of unwound single-strand DNA present [Figure 2].

DNA repair techniques

Today, we know of more than 100 DNA repair enzymes, and it is quite probable that even more remain to be discovered (Cressey, 2015).^[20]

Direct repair

Some forms of alkylation damage are directly reversible by enzymes that transfer the alkyl group from the base of their own polypeptide chain. Mammalian O-methyl-guanine-DNA methyltransferase (MGMT) is capable of repairing the highly mutagenic O-methyl-guanine and O-methyl-thymine lesions from DNA by transferring the methyl group to a cysteine residue in the protein. Since it thereby inactivates itself, MGMT is a suicide protein (Grimaldi *et al.*, 2002; Schipler and Iliakis, 2013).^[21,22]

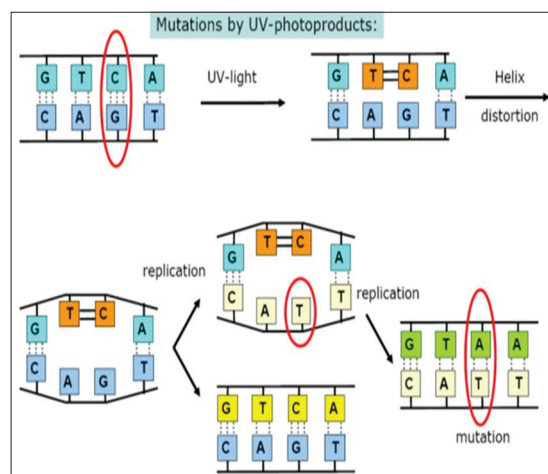


Figure 1: Mutation by UV radiations

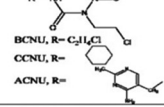
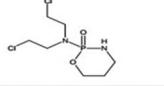
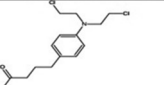
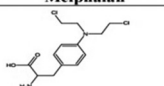
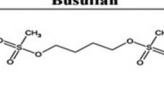
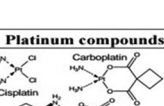
Drug	DNA adduct	DNA repair
BCNU, CCNU, ACNU 	• Monoadducts N¹G, N⁷O⁶G • N¹G:N³C interstrand CL • Intrastrand CLs • DNA-protein CL	• MGMT • FANC pathway (HR, NER) • NHEJ, BER (minor)
Cyclophosphamide 	• N⁷G:N⁷G interstrand CL • N⁷G monoadducts • Phosphotriester monoadducts • Acrolein • DNA-protein CL	• FANC pathway (HR, NER) • MGMT (?)
Chlorambucil 	• N³A, N⁷G monoadducts • N⁷G:N⁷G and N⁷G:N³A (?) • Interstrand and intrastrand CLs • N³A:N³A intrastrand CL • aneuploidy	• BER • FANC pathway (NER, HR)
Melphalan 	• N³A, N⁷G monoadducts • 5'AGT3' interstrand CL • N⁷G:N⁷G and N⁷G:N³A (?) • Interstrand and intrastrand CLs • aneuploidy	• NER • FANC pathway (NER, HR) • BER(?) • NHEJ
Busulfan 	• Monoadducts N⁷G, N³A or N³A (?) • 5'GA3', 5'GG3' intrastrand CL • N⁷G:N⁷G interstrand CL (weak) • DNA-protein CL	• BER • MMR • FANC pathway (NER, HR)
Platinum compounds 	• N⁷G:N⁷G intrastrand CL • 1,2-d(GpG), 1,3-d(GpNpG) • N⁷G:N⁷A intrastrand CL • 1,2-d(ApG) • N⁷G:N⁷G interstrand CL	• NER • MMR • FANC pathway (NER, HR)

Figure 2: List of various alkylating agent responsible for DNA damage

Excision repair

It includes base excision repair (BER) and nucleotide excision repair. BER removes bases that have been damaged by oxidation, ionization radiation, and deamination [Figure 3]. BER system involves an enzyme called N-glycosylase which recognizes the abnormal base and hydrolyse glycosidic bond between it and sugar nucleotide repair system includes three steps, incision, excision, and synthesis. Later, it also includes the activity of DNA polymerase and replicating enzymes. Nucleotide excision repair on the other hand deformation caused by UV and due to the addition of bulky functional groups are treated by firstly unwind them by DNA helicases, and then, endonucleases remove the damage portion. This all is guided by DNA-polymerase (Dantzer *et al.*, 2000)^[23] [Figure 4].

Mismatch base repair

Sometimes, the wrong basis is incorporated during replication, G-T or C-A pairs formed in the daughter strand, therefore, to distinguish a methyl group is tagged on one of the strands during repairing process. DNA polymerase removes the most of incorrectly incorporated bases during replication; mismatch repair is a superfluous system that scans the newly synthesized daughter DNA and excises the mismatched base (Müller and Fishel, 2002)^[24] [Figure 5].

Recombination repair or retrieval system

In thymine dimer or other type of damage, DNA replication cannot proceed properly. A gap opposite to thymine dimer is left in the newly synthesized daughter strand. The gap is repaired by recombination mechanism or retrieval mechanism called also sister strand exchange (Thacker *et al.*, 1986).^[25]

SOS repair mechanism

Sometimes, the replicating machinery is unable to repair the damaged portion and bypasses the damaged site. Used for the DNA damage occur due to topoisomerase poisoning. This is known as translesion synthesis also called bypass system and is emergency repair system. This mechanism is catalyzed by a special class of DNA polymerases called Y-family of DNA polymerases which synthesized DNA directly across the damaged portion (Eller *et al.*, 1997).^[26]

Application of DNA repairs in the treatment of diseases.

Huntington disease (HD)

Human genome is under continuous attack by various harmful agents. However, DNA repair enzymes generally maintain the integrity of the whole genome by properly repairing mutagenic and cytotoxic intermediates, but there are cases in which the DNA repair machinery is implicated in causing diseases rather than protecting against it. When the DNA break occurs at the level of the CHG repeats (form due to trinucleotides formation), DNA polymerase beta was seen to repair the breakage adding multiple copies of the repeat, which is thus expanded. This polymerase is the only one to be significantly expressed in adult neurons and is overexpressed in HD patients. It is the 1st time that a role of DNA polymerase beta in the repair of DNA breaks and in the genesis of Huntington's disease is proposed. If confirmed, new directions for

understanding the pathogenesis of this disease could be provided (Jonson *et al.*, 2013).^[27]

Alzheimer disease

ROS are produced during the respiratory cycle in mitochondria as well as normal cellular and xenobiotics metabolism. These ROS facilitates the degradation and cause lesions in DNA and affects its enzymatic integrity. The patients with Alzheimer disease are lack of BRCA1 levels (due to the attack of ROS), which is a DNA repair factor, which leads to DBS, neuronal shrinkage, synaptic plasticity, impairments, and learning and memory deficits. Scientists also found that if we can increase the level of BRCA1 by stimulating synaptic membrane, then we can treat Alzheimer's disease and prevent its symptoms (Ramamoorthy *et al.*, 2012).^[28]

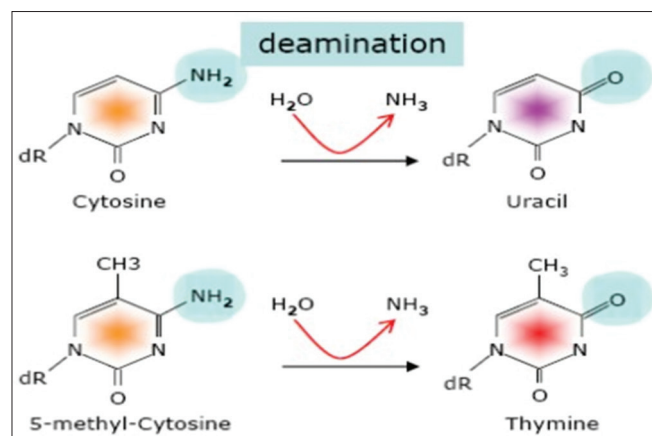


Figure 3: Mutation by deamination

Schizophrenia

This complication starts with the formation of lesions induced by methyl methanesulfonate (MMS), MNNG, and UV-rays. N-nitro-N-nitrosoguanidine (MNNG) and MMS both produce similar types of alkylation, which is so advance that can cause mutations by produce lesions in purines and pyrimidines and further cause schizophrenia. Schizophrenia is a neurodevelopmental disorder where changes in both the hippocampus and memory-related cognitive dysfunctions remain unclear. It is found in the exome study of patients level of RDVs are increased at hippocampus that will help in treatment of hippocampus dysfunctions recollecting the whole of RDVs, but neurodevelopmental dysfunctions are still existed. Due to the decrease level of rsFC level (a chemical that help in proper rate of neurodevelopment and regulate normal functions, so we can treat symptoms such as illusion, delusions, and over aggressiveness but not the disease) (Markkanen *et al.*, 2016).^[29]

Cardiovascular diseases

Proapoptotic activity 53(P53) induced level is the main cause of oxidative stress in cardiomyopathy, atherosclerosis, and heart stroke. It also increases the insulin-resistant factors which directly affect the cardiac health. These problems can solve by DNA repair excision pathways, which guard the genes such as Gadd45 and p48XPE and prevent the initiation of apoptosis in cardiac muscles, thus help in preventing the symptoms and treatments of various heart diseases and also prevent several types of cancer risks (Ishida *et al.*, 2014).^[30]

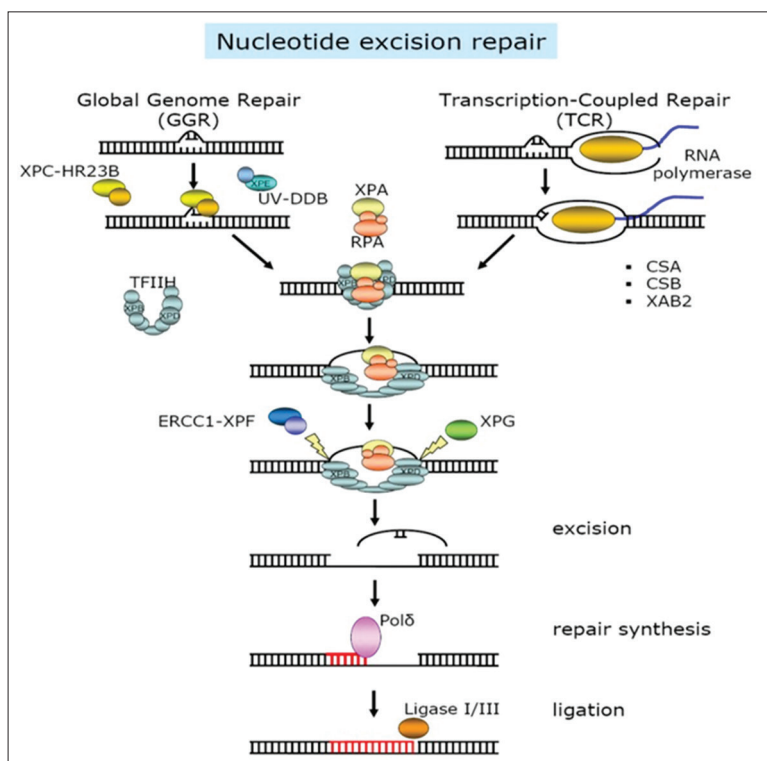


Figure 4: Nucleotide exclusion repair mechanism

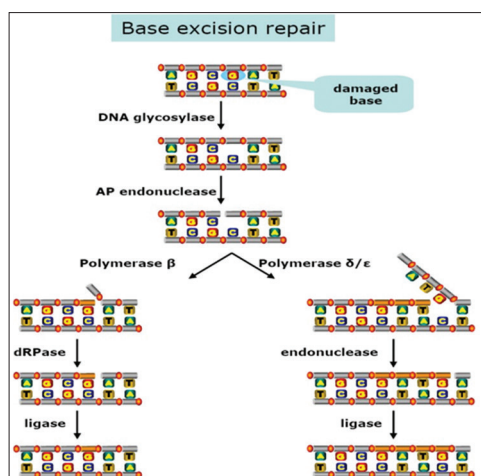


Figure 5: Mechanism of base excision repair

Atherosclerosis

Atherosclerotic plaques contain accumulated activated DNA damage response elements. Studies suggest that this accumulation contains high number of DSBs, which further activates the ATM (discussed earlier) higher in comparison to a normal tissue. This would be treated by BER. It was also found that ROS also plays a major role in this by promoting apoptosis and senescence, but this all was treated by BER and NER (Fetterman *et al.*, 2016).^[31]

DNA repair in cancer therapy

Maintaining proper DNA repair along with chemotherapy can help in the treatment and prevention of several types of cancers. MGMT (O⁶-methylguanine-DNA MGMT) is a suicide enzyme which repairs cytotoxic DNA strands which may affect the action of procarbazine, dacarbazine, streptozotocin, temozolomide, lomustine, nimustine, carmustine, and fotemustine. Thus, the neutralization and maintenance of MGMT and its producing toxic strands can help in chemotherapy and induced its efficiency (Davis and Lin, 2011).^[32]

It can also be done by BER pathway if the cause of cancerous mutation was only SSBs. BER proteins, i.e., APE1 and PARP1 will help in this process. NER help in repair of bulky groups which can help in prevention of *Xeroderma pigmentosum*. Inhibiting DNA polymerases which help in producing cytotoxic DNA strands can also play a major role in prevention and that will also help in the efficiency of chlorambucil and cisplatin. Actually, the problem is the anticancer drugs self-cause the DNA damage too.

Well, these problems may solve by the monofunctional methylating agents, which cause repair of DNA by BER and MGMT, but sometimes multidrug therapy can cause secondary leukemias at this stage, due to processing is done by MMR, causing further mutations.

Topoisomerases inhibitors like several anticancer drugs may help in the prevention and further beyond restart the normal DNA repair process and prevent the occurrence and existence of t-MN.

CONCLUSION

DNA damage is the key of future to treat many of the genetically inherited disorders such as HD, many forms of cancer, diabetes, clinical depression, many of the teratogenic complications, trisomy, and inactivation of several genes. It will be the key to treat the many of the genetic disorders at the starting stage just like in the laboratories by repairing the damaged DNA using several techniques such as polymerase chain reaction, western blotting, southern blotting, eastern blotting, northern blotting, and so many others. It will change the future of many complicated diseases if diagnosed early or in fetal stage.

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