Review Article

DNA mutilation: A telltale sign of cancer inception

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Abstract

DNA damage is a discrepancy in its chemical structure precipitated by a multitude of factors. Most DNA damages can be repaired efficiently through diverse restorative mechanisms subjective to the type of damage. DNA-damaging agents elicit a medley of cellular retorts like cell cycle arrest, followed by DNA repair mechanisms or apoptosis. An unrepaired DNA damage in a nonreplicating cell does not generally engender mutations but a similar scenario in replicating cell routes to permanent modification of genetic material shrugging to carcinogenesis. DNA mutilation can be allied to disarray in bases, debasement of backbone, or crosslinks. Base damages or backbone damages like single-strand and double-strand DNA breaks are usually produced by reactive oxygen species and ionizing radiation. This substantial DNA damage has broadly been considered to be caused by various exogenous and endogenous agents with variable rates of causality and decrees of risk, sourcing toward cancer or other diseases, necessitating furtherance in diagnostics at sequential points. The purpose of this article is to review in detail the various types of DNA damages, their contributory factors, and recent developments in their identification.

Keywords: Abasic, DNA, mutilation, radiation

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INTRODUCTION

DNA contains complex genetic information in a very stable and integrated manner maintained by the presence of highly sophisticated techniques. But the DNA sequence or structure is disrupted as a usual day-to-day event and is reverted by various repair mechanisms. Failure of these repair contrivances turns out to be the primary causal factor for cancer and much other inherited or acquired pathology. The aim of this review is to highlight various types of DNA damages and enumerate their causative factors with a short discussion on recent modalities of damage detection.

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DNA MUTILATION

DNA mutilation or damage can be defined as alterations in the genomic integrity due to severances compelled by various exogenous and endogenous factors. Oxidation, alkylation, or hydrolysis of bases and replication errors are the key endogenous factors that are detrimental to DNA. Such chemical modification of cellular DNA can have profound biological consequences provoking, changes in gene expression, inhibiting cell division, or triggering cell death. In addition, replicative endeavors of damaged DNA can permanently introduce errors into the genetic code and hence, the organic chemistry of DNA has to be stonewalled. Ultraviolet light, ionizing radiation,

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and environmental chemical agents are few among the exogenous factors that may either react directly or indirectly with the DNA.[1]

TYPES OF DNA DAMAGE

1. Rupture of the strand: It can divide into single-strand or double-strand breaks.
   Phosphodiester bond or the bond between the sugar and the base are more disposed for single strand breaks (SSBs). Oxidation of bases or sugars by endogenous reactive oxygen species (ROS) is one of the commonest sources of SSBs with a large proportion caused by •OH. They may occur precisely via disintegration of the oxidized sugar or discursively during patch-up of oxidized bases, abasic sites, or altered bases by base excision repair mechanism (BER). The erroneous or abortive activity of cellular enzymes such as DNA topoisomerase1 (Top1) and unacceptable incorporation of ribonucleotides into DNA are few other sources of SSBs.[2]
   Double strand breaks (DSBs) involve breakage of both strands. The foremost cause of DSB is replication across a nick, giving rise to chromatid breaks during S phase. ROS is the second major cause followed by natural ionizing radiation of the environment and is directly proportional to the radiation dosage. The inadvertent action of nuclear enzymes on DNA and corporeal stress on the DNA duplex are also relevant causatives of DSBs. Enzymatic action of Spo11, a topoisomerase II-like enzyme in meiotic cells is an additional source of DSBs.[3]
2. Abasic sites
   Apurinic or apyrimidinic (AP) sites are the most probable abasic lesions in DNA that are formed by spontaneous hydrolysis of the N-glycosylic bond or as an outcome of elimination of impaired or inapt bases by DNA N-glycosylases. Methylation, oxidation, and deamination of purine or pyrimidine bring in diverse lesions such as N7-methylguanine (N7-meG), 8-oxo-7,8-dihydroguanine (8-oxoG), 5,6-dihydroxy-5,6-dihydrothymine (Tg), or uracil. Confederacy of inapt bases such as uracil during replication and repair or aforementioned DNA damages are removed by specific DNA N-glycosylases yielding AP sites. AP sites that are profusely formed impede DNA replication and transcription and reroute to apoptosis or DNA repair. Furthermore, they are also mutagenic owing to single base-pair substitution or split at AP sites by AP endonucleases/DNA N-glycosylases/AP lyases bringing about SSBs formation with 3 or 5 blocked ends, which can further be converted into awfully perilous DSB after DNA replication.[4]
3. Alteration of bases: Bases can be damaged or destroyed by radiation. Pyrimidines (T, C) are more open to radiation attack than purines.
   Mismatches, deletions, and insertions: Loss of one or more base pairs from the DNA is called deletion. Deletion of one or two bases alters the genetic frame resulting in a distorted nonproductive message. Deletions of three or more bases leave the reading frame intact but a deletion of one or more codons result in a protein missing one or more amino acids which at times could be deleterious. Insertion is the addition of one or more nucleotide base pairs into the DNA sequence most often due to DNA polymerase slippage. They can range from a single base pair inserted incorrectly into a DNA sequence or at times a segment of one chromosome is erroneously inserted into another.[5] The purine and pyrimidine bases in DNA prevail in two different tautomers, one is the common keto form and the other rarer nontautomeric enol form.[6] The common forms of bases may pair with tautomeric form. DNA mispairings can supervene between different tautomeric chemical forms of bases because of a slight shift in the position of the nucleotides in space or because of the presence of an extra proton.
4. Destruction of sugars: The sugar moiety of DNA, deoxyribose, is particularly susceptible to hydroxyl radical damage particularly when these are generated in close contiguity. Site-specific damage by these free radicals leads to oxidation of the deoxyribose moiety tracked by the release of pyrimidines or strand scission. Initially, hydrogen atom abstraction transpires to form a carbon-centered radical that adds

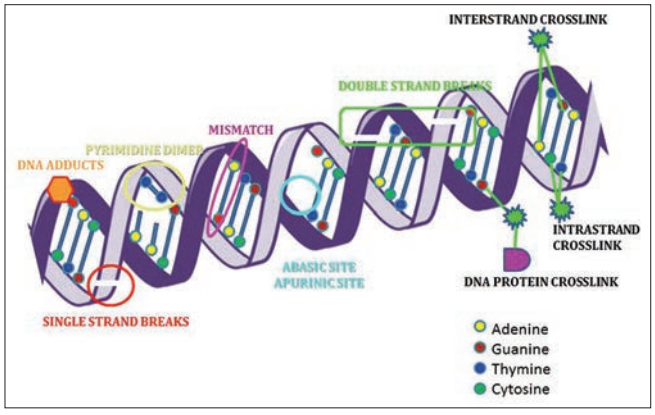

Figure 1: Types of DNA damage. DNA strand breaks, mismatch of bases, abasic sites (apurinic, apyramidinic), dimerization, cross-linking (intrastrand, interstrand, and protein cross-linking), and adduct formation are the various types of DNA damage

an oxygen molecule to form a peroxyl 1'-oxidation in any of the five positions in 2-deoxyribose in DNA. Different products spectra are formed by oxidation of 2-deoxyribose under aerobic and anaerobic conditions. When traces of transition metal ions like iron are present, deoxyribose is cleaved to liberate malondialdehyde. This reactive bifunctional aldehyde can be mutagenic and carcinogenic as it forms adducts to deoxyguanosine and deoxyadenosine. The major adduct to DNA is a pyrimidopurinone called M_1G which gives rise to secondary damaging cellular events. The most common sequential changes were base pair substitutions, transversions, transitions, and frameshift mutations.[7-9]

5. Cross-links and formation of dimers.
   Unsolicited links in DNA can occur in the same strand (intrastrand) or amid two complementary strands (interstrand) or between a base on DNA and a reactive group on a protein (DNA-protein). Interstrand cross-links prevent DNA strand from hewing apart, thus creating an outright impediment to DNA replication and/or transcription summing up to cell death. This contraption of cytotoxic effect is intellectually used currently in anticancer chemotherapy. Bifunctional alkylating agents such as the nitrogen mustards, mitomycin C, platinum compounds, and di- and trinuclear cis-DDP (*cis*-diamminedichlorplatinum) analogs are few drugs that form interstrand cross-links by interacting with the N7 of guanine to form interstrand cross-links. Cross-linking agents typically damage the chromosomes in the manner of a gain, loss, rearrangement of chromosomal segments, or sister chromatid exchanges rather than altering the DNA sequence, that is, they are clastogenic and not mutagenic.[10]
6. Bulky DNA adducts
   DNA adduct is a portion of DNA that is covalently bound to a chemical moiety resulting in abnormal replication and this is the decree of chemical carcinogenesis. N-nitrosamines, aflatoxins, aromatic amines, and polycyclic aromatic hydrocarbons are few classes of carcinogens which form DNA adducts. N-nitrosamine DNA adducts result from either methylation or ethylation of DNA. Minor adducts of alkylating agents like O6-a1kylguanine and O4-a1kylthymine presumably result in mutations and tumor.[11] Humans are exposed to aflatoxins through the consumption of mouldy cereals, grains, and nuts. Aflatoxin BI (AFB1), aflatoxin B2, aflatoxin G1, and aflatoxin G2 are the four major naturally occurring aflatoxins of which AFBI is the most abundant and the most carcinogenic. The metabolic activation of AFBI involves oxidation of the 8,9-olefinic bond to give AFBI-8,9-oxide which reacts with DNA to yield trans-8,9-dihydro-8-(deoxyguanosine-7-yl)-9-hydroxy AFBI. It can undergo depurination or base-catalyzed opening of the imidazole ring to yield pyrimidine adducts. Aromatic amines and amides are generally activated by N-oxidation to yield N-hydroxyarylamines and N-hydroxyarylamides (arylhydroxamic acids), respectively. The stimulation of nitro polycyclic aromatic hydrocarbons is by nitroreduction to N-hydroxyarylamine. N-Hydroxyarylamines can react directly with DNA or be further activated through the formation of acetate and sulphate esters. Typically, major adducts from these electrophilic intermediates are formed through covalent linkage of the amine or amide nitrogen to the C[8] of guanine, whereas minor adducts arise from reactions between carbons in the ortho position in relation to the amine or amide nitrogen and the exocyclic nitrogens and oxygens of guanine and adenine. DNA adduct formation of polycyclic aromatic hydrocarbons (PAHs) normally involves cis or trans opening of the epoxide ring with covalent attachment at the benzylic carbon of the dihydrodiol epoxide. Generally, guanine is the choice for such reactions; however, depending upon the PAH, considerable binding can also occur with adenine and cytosine. Interactions with DNA are clearly nonrandom and sequence specificity for adduct formation has been demonstrated *in vitro* with different chemicals. The magnitude of mutagenic and carcinogenic responses correspond with the enormity of DNA adducts and their potentiality in activation of proto-oncogenes [Figure 1].[12]

ENDOGENOUS FACTORS IN DNA DAMAGE

Oxidative damage to bases

ROS are inherent by-products of customary metabolism of oxygen and they serve as secondary messengers or signalling molecules to regulate biological and physiological processes. Both internal and external factors can lead to dramatically increased founding of ROS which then become deleterious. ROS are profoundly reactive as they contain an unpaired electron in their outer most orbits. ROS include superoxide anion ($O2^-$), hydrogen peroxide (H2O2), singlet oxygen ($^1O_2$), and hydroxyl radicals (.OH). The hydroxyl radical is extremely reactive. Endogenously ROS are formed during mitochondrial respiration where there is single electron transfer in $1 \pm 5\%$ of oxygen liberating superoxide anion ($O2^-$) and chronic infections that elicit an inflammatory response. Acute

inflammatory cells like neutrophils produce superoxide radical and hydrogen peroxide, which form the potent hydroxyl radical subsequently via Haber ± Weiss reaction. These agents can oxidize DNA and the high oxidation potential of guanine residues render it more susceptible relative to cytosine, thymine, and adenine. Oxidation of pyrimidines and purines result in multiple modified bases in DNA. Reaction with a sugar moiety of DNA by hydrogen abstraction gives rise to strand breaks, whereas reaction with aromatic amino acid or amino acid radical of proteins leads to DNA–protein cross-linking, aggregation/fragmentation of proteins, inactivation of proteolytic inhibitors increasing their proteolytic activity, and change in antigenicity of proteins. ROS not only damage the genetic material but also intricate their oxidative effect on the cell membrane which is structurally a bilipid layer. Phospholipids in the cell membrane contain unsaturated fatty acids residue esterified to the 2-hydroxyl group of the glycerol moiety with an incidence of methylene group between two double bonds rendering the fatty acid subtle to oxidation. The initial products of unsaturated fatty acid oxidation are lipid hydroperoxides that are further reduced to unreactive fatty acid alcohols by glutathione peroxidases or to self-reactive epoxides and aldehydes by metal ions. The major aldehyde product of lipid peroxidtion is malondialdehyde which is mutagenic as it reacts with guanine, cytosine, and adenine of DNA to form adducts[13,14] [Figure 2].

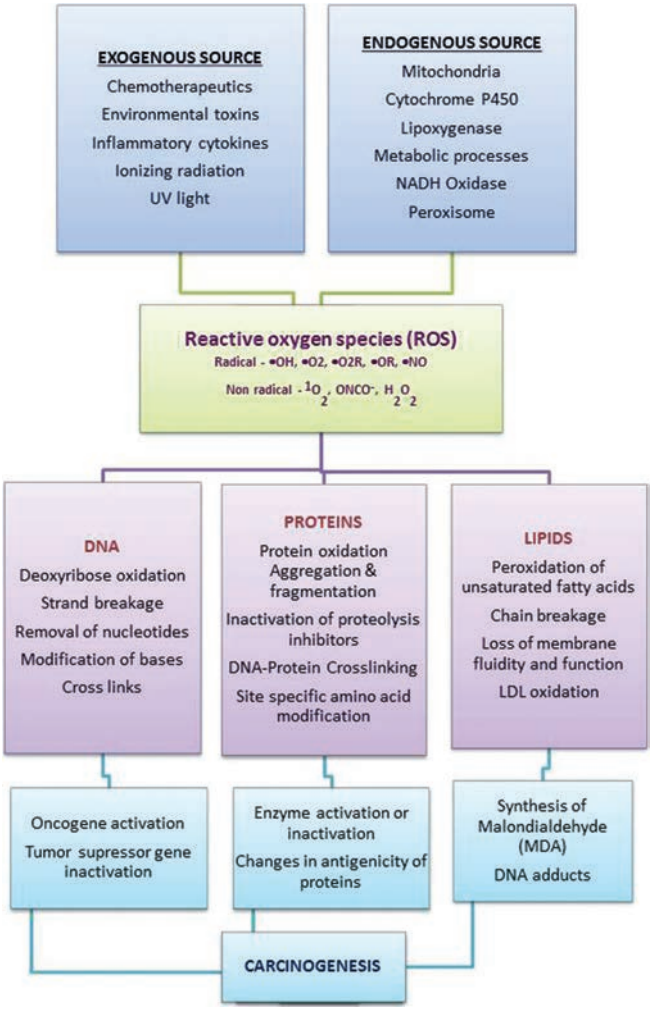

Figure 2: ROS: Source and its enroute to carcinogenesis. A number of exogenous and endogenous factors culminate in ROS formation that eventually precipitates diverse DNA, protein, and lipid mutilations ultimately laying stone for cancer development

To limit mutagenesis and cytotoxicity, the removal of oxidative DNA lesions is mandatory and this is accomplished by various repair mechanisms. Single oxidized DNA base lesions are removed essentially by BER, whereas more complex lesions containing oligonucleotide are processed by nucleotide excision repair. Even after extensive DNA repair, oxidatively damaged nucleotides can be found commonly in cells, not surprisingly, higher in cancer cells.[15] ROS acts both as a damaging and a signalling molecule and the preferential pick depends on the subtle counterbalance between ROS production and scavenging. Enzymic and nonenzymic antioxidants scavenge or detoxify excess ROS. Oxidative stress, that is, an immoderate procreation of endogenous ROS or subsidence in cellular antioxidants inflates the mutation rate and inevitably upscales the cancer risk.[16,17]

Alkylation of bases: Methylation

Oxygen is not the only reason for DNA damage but the transfer of an alkyl group from one molecule to another known as alkylation is also lethal. Transfer of methyl group known as methylation is the most prevailing type of alkylation and is distinct from alkylation in that it specifically transfers a single carbon group, whereas alkylation refers to the transfer of long-chain carbon groups. DNA alkylation refers to the addition of alkyl groups to specific bases, resulting in alkylation products such as O^2-alkylthymine, O^4-alkylthymine, O^6-ethylguanine, O^6-methylguanine, and O^3-methyladenine and the last two being most frequent. The primary sites of alkylation are 0^- and N^- atoms of nucleobases. An alkylating agent is a substance capable of transferring an alkyl group by substituting a free hydrogen atom in an organic compound. Alkylating agents are rationalized into hard and soft. Bifunctional alkylating agents containing two electrophilic centers can cross-link two nucleophilic centers in DNA. Characteristics such as small size, positive charge, and low polarizability which define hard alkylating agents like diazonium ions are highly reactive with hard oxygen nucleophiles in DNA, whereas large, uncharged, polarizable alkylating agents like dialkylsulfates favor reaction with nitrogen centers in DNA. In the guanine residue, N7 position is chiefly nucleophilic and is the preferred site for almost all

small, freely diffusible alkylating agents. Therefore, on one facet DNA alkylation causes DNA damage terminating in cancer and on the other perspective a number of alkylating agents are used in treating cancer. Cells with flawed or subnormal DSB repair mechanism are more susceptible to alkylating agents than competent cells where their action may be astray. Alkylated phosphate that is phosphodiester residue yields phosphotriester that is chemically stable. Alkylation at the exocyclic nitrogen atoms N^2G, N^6A, N^4C, the amidic nitrogens at N1-G, N1-T, and the oxygens at O6-G and O4-T yields chemically stable adducts, whereas alkylation of some endocyclic nitrogens on the nucleobases yields labile lesions that undergo deglycosylation or ring-opening while alkylation at some endocyclic nitrogens also accelerates deamination. N and O atoms in DNA bases are endorsed for the formation of adducts by simple methylating agents. S-adenosylmethionine is a reactive methyl group donor and other simple agents like betaine and choline also carry out endogenous methylation.[18,19]

Hydrolysis of bases

Hydrolytic damage which is the modest form of endogenous DNA damage causes depurination and depyrimidination with consequential abasic sites. The glycosidic bond that holds nucleobases to sugar-phosphate backbone in DNA is more liable to breakage. When compared to pyrimidine bases (cytosine and thymine), the hydrolytic damage is much faster at purine bases (guanine and adenine). The abasic sites thus generate single-strand breaks and in addition the aldehyde residue of the ring-opened form can beget interstrand DNA crosslinks that are highly cytotoxic and mutagenic. A foray of hydroxide on neutral nucleobase or an attack of water molecules on N_3-protonated base may cause hydrolytic deamination. Deamination and methylation processes affect amino-containing bases preferably cytosine while sparingly deaminate adenines to give hypoxanthine. In a cell, daily between 100 and 500 cytosines are deaminated to uracil and moreover deamination of methylcytosine residues occurs faster than unmodified cytosine. Human cells lose about 5,000 adenines or guanines every day because of spontaneous base-sugar link fissions. Such reactions have profound biological consequences resulting in cytotoxicity or mutagenicity of the cells.[19]

Erroneous replication

DNA replication is a fundamental and sternly regulated cellular process that ensures the precise duplication of the cell's genetic material. But mistakes in DNA replication do occur due to insertion of incompetent nucleotide, augmented or paucity of nucleotides in a sequence, or looping/jumping of DNA polymerase. If such deletions include regions containing tumor suppressor genes, it culminates in a mutant cell with malignant competency. Upon entry of a cell into S phase, a wide range of contrivances ensures that the instigation of replication machinery is disabled to avoid rereplication and warrant genome instability. A focal over-replication will result in a gene and if it is possibly an oncogene, the resulting amplification would also be catastrophic. Fortunately, to optimize the likelihood of such errors, the proof-reading machinery comes into play during which the DNA polymerase makes out these errors and replaces them correctly. But this may not be good enough for normal cell functioning. Therefore, after replication also, corrections are done by mismatch repair process further reducing the final error rate. Following mismatch repair, if errors persist, then after the subsequent cell division, they emerge as permanent mutations. Several DNA replication proteins play a decisive role in DNA repair pathways such as BER, nucleotide excision repair, and mismatch repair pathways strategically functioning, depending on the local environment and cellular requirement.[20]

EXOGENOUS FACTORS IN DNA DAMAGE

Damage caused by Physical agents

UV light

Ultraviolet (UV) radiation, composed of three subtypes, UVA, UV-B, and UV-C having different wavelengths is one of the most powerful exogenous agents causing different types of maladies in genomic sequence. Compared with UV-A, UV-B has a shorter wavelength and a more forthright effect on DNA but providentially, UV-B radiation occupies a very trivial part of the total solar energy. It modifies the chemical composition of DNA by forming dimers which disrupt molecular composition. In pyrimidine dimers, two adjacent pyrimidine bases cytosine or thymine are linked atypically perverting the double helical profile of the DNA, thus blocking DNA replication or RNA transcription machinery which could be lethal for a cell. DNA replication is interceded by changing DNA polymerase in thymidine dimers and this TT dimerization is the most confronted form of UV-related damage. UV-A has a petite impact on DNA sequence because of its poor absorption by DNA. But, it indirectly disrupts DNA sequence producing $^1O_2$. Owing to the high absorption in atmosphere UV-C is not of substantial menace to the cells. Electromagnetic radiation can either remove an electron from an atom or can change the energy level of an electron and UV light pursues the later.[21,22]

Ionizing radiation

Radiation with sufficient energy to expel one or more electrons from the orbit in an atom or molecule is ionizing radiation and the process is called ionization. Usually we

classify ionizing radiation as electromagnetic or photon, that is, X rays or gamma rays and particulate or hadron, that is, beta particles, alpha particles, electrons, protons, neutrons, negative π mesons, and heavy charged ions such as the nuclei of argon, nitrogen, carbon (12C), and other elements which interact with the nucleus of the atoms. Radiation differs in its constituent that is electrons, protons, neutrons, and likewise by their energy also. Neutrons or α particles are more destructive as they induce dense ionization along their track called high linear-energy-transfer (high LET), whereas X rays and gamma rays are less destructive as they produce ionizations only sparsely along their track, that is, low LET radiations. Moreover, the DNA damage caused by high-LET radiations is localized and more challenging to repair than the disseminated damage caused by low-LET radiations.[23,24]

Ionizations induced by radiation can happen forthright on the cellular components or collaterally on water molecules, causing water-derived highly reactive free radicals that within a short span react with the nearby cell molecules, bringing about breakage of chemical bonds or oxidation. Radiation is also known to baffle genome integrity producing a wide range of DNA lesions, like damage to nucleotide bases, SSBs, and DSBs.[25] The earliest identified X-ray damage in DNA is the formation of oxidized abasic sites (OAS) that is 2-deoxyribonolactone (dL). Other well-known OAS include 2-deoxypentos-4-close (KA), 3'-phosphoglycolate esters (3'-PG), and 3'-phosphates (3'-P). DNA strand breakage which is the customarily measured indicator of radiation damage results from the formation of OAS. During the formation of OAS, the pioneer deoxyribose-centered radicals can undergo chemical reshuffles that are tempered by the presence of molecular oxygen. dL likely arises from initial hydrogen abstraction from the nucleotide C1' carbon, followed by O2 addition and base loss ultimately leading to strand breaks. At least two other lesions like abasic 2-deoxypentos-4-close without chain breakage or a 3'-PG on one side of a strand break may be initiated by hydrogen abstraction from the deoxyribose C4' carbon.[26]

Ionizing radiation has the capability to engender clusters of DNA damage by generating up to five closely spaced hydroxyl radical pairs that can attack DNA within a small region just with a single radiation track. Clustered lesions constitute 80% of complex damages, while oxidized abasic sites and direct DSBs account for the remaining 20%. Any additional DSBs could potentiate cytotoxic and mutagenic effect.[27,28]

Damage caused by chemical agents

Exposure to chemical agents has been known to induce cancer. Chemicals form adducts with DNA and account for its disruption. They also culminate in cross-links, breakages, and deletions. Some of the important chemical agents are tobacco-specific N-nitrosamine, benzidine, asbestos, benzene, aromatic amines, polycyclic aromatic hydrocarbons, and aflatoxins. Few of these alkylating agents like mustard gas are used as chemical weapon and some like alkyl sulfate-ester, sulfonic-esters, N-nitroso-compound, halogenated hydrocarbon, and epoxides are widely used in industry. Grossly all of the alkylating agents are capable of transferring one or two alkyl groups to the nucleophilic position of the DNA bases and hence are electrophilic compounds. When they react with two nucleophilic sites of DNA it results in cross-linking within a DNA strand or with another strand or with exogenous or endogenous protein compounds.[29] Although not directly, some of the heavy metal ions also induce oxidative damage to the DNA.

Base molecular isomerization where there is a shift in the position of hydrogen bonds between base pairs also induces DNA damage by mismatching the bases during replication. Metabolites of fungi such as aflatoxins are toxic and carcinogenic with variable potency in several animal species. As described earlier, Aflatoxin B1 (AFB1) which is the secondary metabolite of Aspergillus flavus and Aspergillus parasiticus that contaminate various food resources such as rice, wheat, maize, corn, and peanuts stored in warm and humid places are toxic and are acclaimed as human hepatocarcinogens. Aflatoxin B1 forms DNA, RNA, and protein adducts with guanine in human hepatocytes and also causes transversion mutations (G: C to T: A) impairing DNA, RNA, and protein synthesis and ultimately culminating in hepatocellular carcinogenesis.[30,31]

DETECTION OF DNA DAMAGE

Delineating the damage site of DNA can be done using any of the molecular structure study methods. Promptness, good reproducibility, economical, formidable competency, and finally no isotopic pollution are the factors that could be contemplated while making a choice of the method. Comet assay or single cell electrophoresis is a rapid, sensitive, simple, and widely used method for DNA damage detection such as strand break damage, DNA crosslinking damage, or other single-cell DNA damage. The core perception of comet assay is that undamaged DNA retains an extremely structured association with matrix proteins in the nucleus. When the DNA is damaged, there is disharmony in the constitutional framework resulting in loss of compactness of individual strands, spreading

out of the cavity into the agarose. Subsequently, when an electric field is applied, the undamaged DNA strands are too large and do not leave the cavity, whereas the damaged fragments of DNA leave the cavity. The amount of DNA that leaves the cavity and how far it moves in a given period of time is a measure of the amount of DNA damage in the cell. Pulsed-field gel electrophoresis can be used for the detection of DNA DSBs. Denaturing gradient gel electrophoresis can be used to detect the point mutation in DNA fragments and the most commonly used PCR single-strand conformation polymorphism analysis can be used to detect 70%-95% of the mutations, although the site and property of the mutation cannot be established.[29]

Fluorescent spectrophotometry is used to detect the DNA adducts and high-performance liquid detects the single nucleotide polymorphisms and heritable mutations. Competitive immunoassay, solid-phase competition assay or noncompetitive enzyme-linked immunosorbent assay methods, and ultra-sensitive enzymatic radioimmunoassay can be used for DNA adducts detection. Cleaving enzyme fragment length polymorphism analysis is a new type of gene mutation detection method, which can detect the gene mutation on the DNA fragments more than l kb in length. Moreover, it shows great superiority as the technique is simple and gene mutation can be accurately determined with good reproducibility. Allele-specific amplification method, which is based on PCR technology, is a kind of single nucleotide mutation detection method and can conventionally analyze the replacement of known bases or small fragments absence mutation and insertion mutation. DNA chip and molecular probes developed in recent years are new methods for detecting DNA damage. The 32P-post-labeling method can detect the DNA adducts, even if the structure of adducts is unknown.[29]

CONCLUSION

The aim of the review was to assimilate facts on the spectrum of DNA damage induced by a plethora of exogenous and endogenous agents that persuade chemical modification of cellular DNA. It is clear that the modulations in DNA prompt change in gene expression and acquire strategies to deter cell division and trigger repair or cell death.

The ability to repair complex and diverse lesions arbitrate the eventual fate of the cell. Diversely any attempts to replicate damaged DNA can introduce mutations into the genetic code and culminate in cancer.

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Conflicts of interest
There are no conflicts of interest.

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