

Original Article

DNA damage in cancer development: special implications in viral oncogenesis

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Abstract: DNA lesions arise from a combination of physiological/metabolic sources and exogenous environmental influences. When left unrepaired, these alterations accumulate in the cells and can give rise to mutations that change the function of important proteins (i.e. tumor suppressors, oncoproteins), or cause chromosomal rearrangements (i.e. gene fusions) that also result in the deregulation of key cellular molecules. Progressive acquisition of such genetic changes promotes uncontrolled cell proliferation and evasion of cell death, and hence plays a key role in carcinogenesis. Another less-studied consequence of DNA damage accumulating in the host genome is the integration of oncogenic DNA viruses such as Human papillomavirus, Merkel cell polyomavirus, and Hepatitis B virus. This critical step of viral-induced carcinogenesis is thought to be particularly facilitated by DNA breaks in both viral and host genomes. Therefore, the impact of DNA damage on carcinogenesis is magnified in the case of such oncoviruses via the additional effect of increasing integration frequency. In this review, we briefly present the various endogenous and exogenous factors that cause different types of DNA damage. Next, we discuss the contribution of these lesions in cancer development. Finally, we examine the amplified effect of DNA damage in viral-induced oncogenesis and summarize the limited data existing in the literature related to DNA damage-induced viral integration. To conclude, additional research is needed to assess the DNA damage pathways involved in the transition from viral infection to cancer. Discovering that a certain DNA damaging agent increases the likelihood of viral integration will enable the development of prophylactic and therapeutic strategies designed specifically to prevent such integration, with an ultimate goal of reducing or eliminating these viral-induced malignancies.

Keywords: DNA lesions, DNA damaging agents, mutations, genomic instability, carcinogenesis, oncoviruses, viral-induced malignancies, viral integration

Introduction

DNA is the biological template needed for an organism to develop, function, grow, and reproduce. Its integrity and stability are therefore vital to life. However, due to its dynamic nature, this macromolecule is constantly subjected to several alterations. In fact, it has been estimated that each cell of the human body receives approximately 70,000 DNA lesions per day [1, 2]. These aberrations arise from physiological or metabolic sources, as well as exogenous environmental influences [3, 4]. Depending on the source or cause of DNA damage, the lesions can range from simple base changes to more complex alterations including single- or double-stranded breaks [5]. To avoid detrimental consequences to cellular functions and hence survival, life has evolved

several systems that maintain genetic stability under strict control. Indeed, in addition to the proofreading activity of the DNA polymerases that correct mis-incorporated bases during replication, cells possess various DNA repair mechanisms to restore the damaged molecule [6, 7]. Unfortunately, not all DNA lesions are efficiently repaired in an error-free manner, leading to the acquisition and accumulation of many mutations which can ultimately contribute to several diseases, including cancer [8, 9]. The relevance of DNA damage in carcinogenesis became particularly apparent when it was recognized that almost all carcinogenic agents are also mutagenic, causing changes in the DNA sequence [10]. In recent years, DNA damage and repair processes have also received a special attention in the case of

oncogenic viruses, since the process of malignant transformation by several of these viruses, including Hepatitis B virus (HBV), Merkel cell polyomavirus (MCV) and Human papillomavirus (HPV), is likely dependent on DNA damage promoting viral integration into human genome [11, 12]. In this paper, we review the various endogenous and exogenous factors that cause different types of DNA damage and discuss the contribution of these lesions to cancer induction. Finally, we shed the light on the amplified effect of DNA damage in viral-induced carcinogenesis.

Sources and types of DNA damage

Based on the origin of the insult, DNA damage is classified into two main groups, namely endogenous and exogenous DNA damage. Endogenous DNA lesions are caused by cellular metabolic processes such as oxidation, hydrolysis, alkylation, and polymerase incorporation errors, whereas exogenous sources of DNA damage include environmental factors such as IR, UV radiation, and various chemical agents. Here we present a brief overview of the main endogenous and exogenous agents causing different types of DNA damage (summarized in **Table 1**).

Endogenous DNA damage

Oxidative DNA damage

One of the most prominent sources of DNA damage is reactive oxygen species (ROS). These chemically reactive molecules containing oxygen are produced endogenously as common byproducts of aerobic cellular respiration, and are also derived from catabolic oxidases, anabolic processes, and peroxisomal metabolism. ROS can also be induced by various exogenous sources such as UV light, ionizing radiation, diet, stress, pathogens, and smoking [13, 14]. At low or moderate levels, these free radicals play essential physiological roles in intracellular cell signaling and homeostasis, cell death, immune defense against pathogens, and induction of mitogenic response. However, in excess, they can cause oxidative damage to the biological macromolecules, severely compromising cell health and contributing to disease development [15-17]. For this reason, cells are equipped with several systems to protect the cellular components and mitigate the

deleterious effects of ROS. For instance, aerobic respiration is confined to the mitochondrial compartment, thereby protecting the other cellular elements. Furthermore, the DNA is wrapped around complexes of histones, giving the chromosome a more compact shape, thereby protecting it from oxidizing effects. Most importantly, redox homeostasis is maintained by two arms of antioxidant defense machineries: enzymatic components (i.e. superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferase) and non-enzymatic, low molecular weight compounds (i.e. glutathione, vitamin A, vitamin C, vitamin E) [3, 18, 19]. When the balance between ROS production and antioxidant defense mechanisms are disrupted, oxidative stress occurs, causing damage to the DNA, proteins, and lipids.

Approximately 100 different oxidative DNA base lesions can be generated by excessive production of ROS [20-22]. Some of the most common and biologically significant oxidative base modifications include 7,8 dihydro-8-oxoguanine (8-oxoG), thymine glycol (TG), 8-hydroxyadenine, 5-hydroxymethyluracil, 2,6-diamino-4-hydroxy-5-formamidopyrimidine and 4,6-diamino-5-formamidopyrimidine (commonly called Fa-Pys), and cyclopurines [23, 24]. Depending on their chemical composition, these base lesions can either serve as a miscoding template causing mutagenesis or they can block DNA and RNA polymerase complexes thereby inhibiting DNA replication and transcription. For example, 8-oxoG pairs incorrectly with adenine instead of cytosine, causing G→T transversions and thereby adding to the mutational load [25, 26]. On the other hand, the “bulky” adducts such as cyclopurines cause DNA helix distortion and therefore block DNA or RNA polymerase progression [27, 28]. As for 5-hydroxymethyluracil, the oxidation of the methyl group of thymine hinders the binding of AP-1 transcription factors to DNA [29, 30].

In addition to oxidation of the DNA bases, ROS radicals also cause single-strand DNA breaks (SSBs). It is estimated that oxidative stress generates around 2,300 SSBs per cell per hour [3]. This highly common type of DNA damage involves the breakage of the phosphodiester backbone in one of the DNA strands and often harbors single nucleotide losses or non-conventional damaged termini such as 3'-phos-

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Table 1. Endogenous and exogenous sources of DNA damage, types of DNA lesions produced, repair mechanisms activated, and consequences on the DNA structure and processes

	Damaging event	Major forms of lesion	Repair mechanisms	Consequences on DNA
Endogenous factors	Oxidation (ROS)	Oxidative base modifications	Base excision repair	Serve as miscoding template causing mutagenesis; helix distortion
		SSBs	Single strand break repair or double strand break repair pathways	Collapse of DNA and RNA polymerase complexes; recombination events
	Alkylation (SAM)	Methylated bases	Direct reversal; base excision repair; mismatch repair	G→A and T→C mutations; Inhibition of DNA replication
	Hydrolysis	AP sites	Base excision repair; lesion bypass	Misincorporation of bases; DNA or RNA polymerase block
	Polymerase incorporation errors	Deaminated bases (uracil) Base substitutions, insertions or deletions	DNA glycosylase & base excision repair Mismatch repair	Changes in coding properties causing mutagenesis Mutagenic outcomes and genomic instability; fork collapse
Exogenous factors	Ionizing radiation	DSBs	Non-homologous end-joining; Homologous recombination	Mutagenesis, chromosomal translocation and rearrangements; genomic instability
		SSBs	AP endonucleases	Polymerase block
		Single base alterations (mostly oxidation)	Base excision repair	
	Ultraviolet radiation	CPDs and 6-4PPs	Nucleotide excision repair	Mutagenicity (C to T and T to C transversions and CC to TT transition mutations); helix distortion; error-prone bypass
Chemical agents (<i>aromatic amines, alkylating agents, PAHs, reactive electrophiles, natural toxins, chemotherapeutic agents</i>)	Base lesions and DNA adducts	Nucleotide excision repair; direct reversal; base excision repair; mismatch repair	Base substitutions; frameshift mutations; replication and transcription block; destabilization and breakage of DNA; helix distortion	
		Intrastrand or interstrand crosslinks	Nucleotide excision repair; homologous recombination	Structure disruption; inhibition of DNA replication and transcription

phate, 3'-phosphoglycolate, or 5'-hydroxyl groups. Consequences of such damage are collapse of DNA or RNA polymerase complexes, as well as recombination events during replication. Consequently, if SSBs are not repaired rapidly, they can lead to cell death, chromosomal aberrations, and genetic mutations [23, 31]. While oxidized bases are commonly repaired by the base excision repair (BER) mechanism, DNA breaks are repaired by the single strand break repair (SSBR) or double strand break repair (DSBR) pathways [32-34].

Finally, oxidative damage to other cellular macromolecules such as lipids also produce additional forms of DNA damage. In fact, lipid peroxidation (LPO) products are responsible for about 1 adduct per 10^6 - 10^7 DNA bases [35-37]. For instance, malondialdehyde (MDA), generated as one of the final products of polyunsaturated fatty acid peroxidation, can interact with DNA bases to form mutagenic bulky adducts such as pyrimido[1,2 α]purin-10(3H)-one (M_1G), or induce the generation of a covalent inter-strand crosslink. Both of these generated lesions create structural alterations in the DNA molecule, thereby inhibiting replication or transcription machinery of the cells [38, 39]. Another major lipid peroxidation-derived aldehyde, 4-hydroxy-2-nonenals (4-HNE), can also react with the DNA to form four diastereomeric 1,N2- γ -hydroxypropano adducts of deoxyguanosine (HNE-dG), preferentially at the mutational hotspot codon 249 of the human p53 gene, and therefore these LPO products have been associated with p53 mutation-related cancers [40, 41]. Removal of the different types of LPO-induced adducts from the DNA molecule is achieved by several repair systems, including direct reversal, BER, nucleotide excision repair (NER), and recombination [42].

Alkylating DNA damage

Besides ROS, several other small reactive molecules endogenously present in living cells can cause DNA damage. S-adenosyl-L-methionine (SAM), commonly used as a reactive methyl group donor by methyl transferases, is involved in DNA methylation reactions crucial for gene regulation [43]. However, like any reactive compound, this alkylating agent can spontaneously modify DNA bases to generate harmful adducts. It is estimated that up to 4,000 7-methylguanine, 600 3-methyladenine

and 10-30 O6-methylguanine residues are formed per cell per day in mammals. SAM also produces two other minor mutagenic methyl lesions, 3-methylthymine and 3-methylcytosine [44, 45]. While SAM is the most prominent type of alkylating agent, other examples of endogenous compounds that induce methylated DNA lesions include nitrosated bile salts, betaine, and choline [46]. Furthermore, alkylating DNA damage can be originated by exogenous sources such as tobacco smoke, environmental pollution, and diet (such as nitrate- or nitrite-containing food) (*discussed later in Section II-B-3b*) [45, 47].

7-methylguanine residues are relatively harmless since they do not cause any alterations in the coding specificity of the guanine base. However, the destabilization of the glycosidic bond due to N-7 substitution on guanine can result in a spontaneous cleavage generating a mutagenic apurinic (AP) site and imidazole ring opening, which interferes with DNA replication [48, 49]. Similarly, 3-methyladenine is partly cytotoxic due to its ability to inhibit DNA synthesis [50, 51]. In contrast, O6-methylguanine and the related residues O4-methylthymine and O4-ethylthymine residues mispair during DNA replication, causing G→A and T→C transition mutations, respectively. Therefore, if left unrepaired, these methylated DNA bases are a major source of mutagenic and genotoxic lesions [52-54]. Methylated bases are typically repaired by one of two main pathways: direct reversal by O6-methylguanine-DNA methyltransferases and the BER pathway. In cases of abnormal base pairing with other residues, mismatch repair (MMR) may also be triggered [55-58].

Hydrolytic DNA damage

Endogenous DNA damage can also result from hydrolytic processes occurring under physiological conditions. As a molecule within an aqueous milieu, the covalent structure of the DNA is unstable and subject to hydrolytic reactions. DNA hydrolysis can result in spontaneous formation of apurinic/apyrimidinic (AP) sites, or deamination of individual bases [59].

Abasic or AP sites are generated in the DNA when water molecules attack and cleave the N-glycosidic bond between the bases and the sugar phosphate backbone. The generation of

these DNA lesions can further be induced by ROS radicals or alkylating agents [60]. AP sites are also produced as an intermediate in the BER pathway when a DNA glycosylase removes the damaged base [61, 62]. In humans, abasic sites are one of the most common types of endogenous DNA lesions, with an estimated 10,000 AP sites created per cell per day [63, 64]. Because they lack the instructional information, AP sites can cause mutations due to misincorporation of bases (preferentially adenine) opposite the non-coding abasic site during semi-conservative replication [65, 66]. Furthermore, they can block DNA or RNA polymerases and inhibit DNA replication and transcription respectively [67]. Due to their unstable nature, abasic sites are also often converted into SSBs from a β -elimination reaction [68, 69]. The BER pathway is the major mechanism for the repair of AP sites, while translesion DNA synthesis, also referred to as lesion bypass, is used as a secondary defense mechanism against these abasic lesions [70].

The second type of hydrolytic process that causes endogenous DNA damage is called spontaneous deamination. During this reaction, water molecules attack and replace exocyclic amine groups of the individual bases, converting cytosine, adenine, guanine, and 5-methylcytosine into uracil, hypoxanthine, xanthine, and thymine, respectively [71]. In addition, the rates of base deamination may be stimulated by environmental exposure to UV radiation, intercalating agents, nitrous acid, and sodium bisulfite [72-75]. Cytosine and its homologue 5-methyl cytosine are the preferential targets of hydrolytic deamination. Around 100-500 cytosines are deaminated to uracil per cell each day, whereas 5-methylcytosine is deaminated to thymine 3-4 times more rapidly than cytosine [3, 71, 76]. Since hydrolytic deamination introduces changes in the coding properties of the original bases, it is considered a major source of spontaneous mutagenesis in humans. For instance, cytosine deamination causes the alteration of original C:G base pairing into a U:A base pair in the first round of replication, which then results in a CG→TA mutation, a feature that underlies the common cancer-associated C/T mutational signature. On the other hand, deamination of 5-methylcytosine results in a G:T base pairing, causing GC→AT transition at the CpG sequences [77-80]. While deaminated cytosine is excised from

the DNA by uracil-DNA glycosylase generating an AP site that is efficiently corrected via the BER pathway, the lesion caused by 5-methylcytosine deamination is a substrate for the thymine-DNA glycosylase or the relatively slower mismatch repair (MMR) process [81-84].

Damage from polymerase incorporation errors

Faulty DNA replication is another source of endogenous DNA damage. With every DNA replication, 3×10^9 nucleotide bases are copied by DNA polymerases in humans. These enzymes also fill the gaps generated during several DNA repair mechanisms such as BER, NER, and MMR [85]. While some DNA polymerases (particularly δ and ϵ) synthesize DNA at a high fidelity, others copy bases at a lower fidelity during DNA replication or repair processes. It is estimated that despite a highly evolved replication apparatus, base incorporation errors occur at a frequency of 10^{-6} to 10^{-8} per cell per generation [86-88]. Replication errors that escape the proofreading activity of replicative polymerases result in inaccurate base substitutions and single base insertion/deletion errors in the newly synthesized DNA strand. If these errors are not quickly and accurately repaired by the MMR pathway, they become incorporated into both strands during the next replication cycle, thereby leading to a change of DNA sequence and mutagenic outcomes [88, 89]. Additionally, replicative polymerases can mis-incorporate uracil instead of thymine opposite adenine in the DNA due to alterations in the concentration of the nucleotide pool within the cell's environment. Although U:A base pairing follows "normal" Watson-Crick geometry and does not cause any distortion, it still requires repair by uracil-DNA glycosylase since the methyl group of thymine is essential to bind with DNA-binding proteins in the major groove of the DNA [90-92]. Finally, replication errors can also accumulate from strand slippage events, particularly in repetitive sequences such as microsatellites (stretches of 2-6 nucleotide repeats), since nearby repetitive bases can stabilize the incorrect base pairing and allow DNA replication to resume, causing insertion and deletions of nucleotides that can potentially change the reading frame [23, 93, 94]. Worse, replication through microsatellite sequences or transcription-derived R-loops can lead to replicative stress, leading to fork collapse, double-strand

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DNA breaks (DSBs), and genomic instability [95-98]. Cells have evolved several checkpoint pathways that examine the internal and external cues and respond to potential failures. The S phase checkpoint in particular constitutes the surveillance mechanism that ensures successful DNA replication, preventing genomic instability upon replication stress [99, 100].

Exogenous DNA damage

Ionizing radiation

Ionizing radiation, composed of alpha, beta, gamma, neutrons, and X-rays, is considered a major physical agent with DNA-damaging effects and is ubiquitous in our environment. Common sources of exposure to IR involve cosmic rays from outer space, radioactive materials in rocks and soil, and medical devices used for diagnosis and therapy [101, 102]. IR can cause damage to the DNA by its direct interaction with the molecule, thereby disrupting the physical structure of the molecule. This type of damage accounts for 30-40% of IR-induced lesions. The remainder of the IR-induced DNA lesions are caused indirectly via radiolysis of water molecules generating free radicals that in turn cause oxidative damage to the DNA [103-105]. Hence, depending on the type and dose of exposure, IR can induce a spectrum of DNA damage lesions ranging from single base alterations (such as oxidation, alkylation, deamination, AP sites) to DNA-protein crosslinks, DNA-DNA crosslinks, SSBs and DSBs. For instance, studies have shown that each Gy of gamma radiation generates approximately 850 pyrimidine lesions, 450 purine lesions, 1,000 SSBs and 20-40 DSBs per cell [106-109].

Because ROS radicals account for about 60-70% of the IR-induced DNA damage, the base lesions produced by IR are, as expected, very similar to those generated by oxidative stress discussed earlier (see *Section II-A-1*). In contrast, SSBs induced by IR have a unique signature containing 3' phosphate or 3'-phosphoglycolate ends rather than the usual 3'-OH ends at the DNA breaks. These modified ends are typically processed and repaired by AP endonucleases, polynucleotide kinases/phosphatases, and tyrosyl DNA phosphodiesterases [110-113]. Finally, DSBs, usually induced in clusters by IR, are considered to be the most

important and dangerous of these lesions due to their high cytotoxic and mutagenic ability. Generated from multiple damaged sites that are closely positioned on both DNA strands, they lack an undamaged complementary strand that could be used as a template during repair [114, 115]. Consequently, these DSBs are usually repaired without a template via non-homologous end-joining (NHEJ), resulting in deletion/insertion mutations as well as chromosomal translocation and rearrangements at the repair junctions. In those cases where they can seek a repair template such as sister chromatids during S/G2 phases or homologous chromosomes, DSBs can also be repaired by homologous recombination (HR). Although this repair mechanism is more accurate, translocations, inversions, deletions, and large-scale loss of heterozygosity can still occur from the associated crossover events [116-119].

Ultraviolet radiation

Exposure to ultraviolet radiation is another common environmental health hazard that causes DNA damage and alters the genomic integrity of an organism. Based on the range of wavelength, UV radiation is classified into three categories: UV-A (315-400 nm), UV-B (290-315 nm), and UV-C (280-100 nm). While UV-C is absorbed by the ozone layer, UV-A and UV-B are able to penetrate the Earth's atmosphere and therefore comprise the primary damaging components of the solar UV spectrum, posing a great concern to humans [120].

The DNA molecule is most susceptible to UV damage at its relatively flexible areas. In fact, the p53 gene is considered to be one of the hot spots for UV-induced lesions [121]. This non-ionizing radiation causes two major types of DNA lesions, cyclobutane pyrimidine dimers (CPDs), and pyrimidine (6-4)-pyrimidone photoproducts (6-4PPs), at a rate of 10^5 DNA photolesions per hour in an exposed cell [122]. CPDs are produced when two adjacent pyrimidine bases become covalently linked to create a cyclic ring structure. On the hand, 6-4PPs are generated from a noncyclic covalent bond formed between the 5' end of C6 and 3' end of C4 of adjacent pyrimidines via spontaneous rearrangement of the unstable intermediates, oxetane (when the 3'-end is thymine) or azetidene (when the 3'-end is cyto-

sine) [120, 123, 124]. 6-4PP adducts can also undergo isomerization to their Dewar form following exposure to another light photon from UV-A or UV-B, while reverting back to the conventional 6-4PP structure when exposed to UV-C radiation [125, 126]. Although 6-4PPs make up around 1/3rd of the total UV-induced DNA modifications, they have a greater potential to cause mutagenesis [23]. CPDs and 6-4PPs are usually repaired by the specialized UV-induced DNA damage repair system called NER; but if left unrepaired, they result in cytotoxicity and mutagenicity [127]. Both of these bulky dimers distort the structure of the DNA helix, introducing bends that can hinder transcription and replication, requiring translesion polymerases to bypass them, thereby contributing to mutagenic load [128]. The most common mutations induced by pyrimidine dimers include C to T and T to C transversions followed by the characteristic tandem CC to TT transition mutations [129, 130]. In addition to its direct effect on pyrimidine bases, UV radiation can also induce modifications to the DNA purine bases but to a very low extent (1×10^{-5} in native DNA). For instance, photoproducts such as adenine dimer and Pörschke photoproduct (an adenine residue that has undergone photocycloaddition reactions with adjacent adenine or thymine) have been reported following UV-B radiation [131, 132]. Furthermore, UV radiation can also cause damage to the DNA indirectly through generation of ROS particles by photosensitizing reactions. These free radicals oxidize the DNA bases such as guanine causing G-T transversions as discussed earlier in the “oxidative DNA damage” section. Other oxidation products induced upon exposure of DNA to UV radiation include 8-oxo-Ade, 2,6-diamino-4-hydroxy-5-formamidoguanine (FapyGua), FapyAde, and oxazolone [120, 133, 134]. DNA strand breakages and DNA-protein and DNA interstrand crosslinks have also been documented in UV-exposed cells [135-138].

Exogenous DNA-damaging agents

In addition to ionizing radiation and UV radiation, in our daily lives we are exposed to numerous extrinsic DNA-damaging agents that create a massive diversity of DNA adducts. Exogenous sources of these agents include industrial and environmental chemicals, dietary products (including food preservatives and additives), and

pharmaceutical agents. Due to the space restriction and scope of this manuscript, we will briefly discuss about the most important extrinsic DNA-damaging agents.

Aromatic amines: Aromatic amines, such as 2-aminofluorene and its acetylated derivative N-acetyl-2-aminofluorene, are found in cigarette smoke, fuel, coal, industrial dyes, synthetic chemical insecticides, and high temperature cooking. These aminofluorenes are activated by the P450 monooxygenase system into carcinogenic ester and sulfate alkylating agents, which attack the C8 position of guanine to cause C8-guanine lesions. If not repaired by the NER pathway, these adducts ultimately lead to base substitutions and frameshift mutations [139-144].

Exogenous alkylating agents: In addition to the endogenous alkylators naturally occurring in the cells (discussed in Section II-A-2), several alkylating agents are produced exogenously from diet components, tobacco smoke, industrial processing, biomass burning, and chemotherapeutic agents. As discussed earlier, alkylating agents react with great affinity to the highly nucleophilic base ring nitrogens and spontaneously modify DNA bases to generate methylated DNA lesions, including modified adenine (at N1, N3, N6 and N7), guanine (N1, N2, N3, N7 and O6), cytosine (N3, N4 and O2), thymine (N3, O2 and O4). Moreover, bifunctional alkylating agents can also cause formation of intrastrand or interstrand crosslinks that adversely impair replication or transcription [3, 145-148].

Polycyclic aromatic hydrocarbons: Polycyclic aromatic hydrocarbons (PAHs) are potent atmospheric pollutants present in cigarette smoke, car exhaust fumes, charboiled food, and incomplete combustion of organic matter and fossil fuels. Examples of PAHs include naphthalene, anthracene, pyrene, 1-hydroxypyrene, 1-nitropyrene, dibenzo[a,l]pyrene, and benzo(a)pyrene, with the latter being the most studied [149, 150]. Composed of carbon compounds with two or more aromatic rings, PAHs are activated by cytochrome P450 system as well as photooxidation, one electron oxidation, multiple ring-oxidation, and nitrogen-reduction pathways, to generate reactive intermediates that cause damage to the DNA [151-153]. Activated benzo(a)pyrene produces the carcinogen (+)-anti-

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BPDE [(+)-7,8-hydroxy-9 α , 10 α -epoxy-7,8,9,10-tetrahydrobenzo(α)pyrene], and the (+)-anti-BPDE and the (-)-anti-BPDE intermediates, which intercalate into the DNA and bind to guanine at the N2 exocyclic position to form BPDE-N2-dG DNA adducts. If left unrepaired by NER and BER pathways, these lesions lead to G/T transversion mutations and harmfully affect replication, resulting in cancer development [154-157]. Indeed, many PAH-related mutation signatures have been reported in the tumor suppressor gene p53 [158-160].

Other reactive electrophiles: There are several other prominent reactive electrophiles that cause DNA damage and induce carcinogenesis. For example, N-nitrosamine, encountered by humans from tobacco smoke and preserved meats, is a potent carcinogen that has been linked with esophageal, gastric, and nasopharyngeal cancers. Formed by a reaction between nitrates or nitrites and certain amines, this compound alkylates N-7 of guanine, leading to destabilization and increased breakage of DNA, thereby causing toxic and mutagenic effects [161-164]. 4-nitroquinoline 1-oxide is another reactive electrophile naturally occurring in the environment, with mutagenic properties in oral carcinogenesis. This compound is activated to 4-acetoxyaminoquinoline 1-oxide which causes the formation of C8-guanine, N2-guanine, and N6-adenine covalent adducts, as well as oxidative DNA lesions such as 8-hydroxyguanine [165-167]. Another remarkable electrophilic compound is the estrogen hormone, commonly used in hormonal replacement therapy. Prolonged use of this hormone has been reported to increase risks of breast cancer due to its DNA damaging nature. Upon its hydroxylation by the P-450 1B1 enzyme complex, estrogen is converted into reactive catechol estrogens, which either become oxidized to semiquinones and quinones that react with purines at the N3 and N7 positions, or they generate free radicals, ultimately leading to AP sites and strand breakages [168-171].

Natural toxins: Aflatoxins (B1, B2, G1, G2, and M1), produced by pathogenic fungi such as *Aspergillus flavus* and *Aspergillus parasiticus*, have been associated with increased risk of liver cancer [172-174]. Humans are exposed to these genotoxic and carcinogenic compounds from contaminated cereals, oilseeds, spices,

tree nuts, and milk products [172]. Following dietary or inhalation exposure, the most prevalent and potent aflatoxin B1 (AFB1) is activated by the P450 complex into aflatoxin B1-8,9-epoxide which alkylates guanine to generate an AFB1-N7-guanine adduct. The latter weakens the glycosidic bond and causes depurination or is further hydrolyzed to form AFB1-formamidopyrimidine, which causes less DNA distortion but still blocks replication with a greater G/T transversion potential [175-177].

Chemotherapeutic agents: Chemotherapeutic agents are intentionally employed in clinical settings to treat patients suffering from different types of cancer. Several of these anti-cancer drugs exert their effect through DNA damage, including cisplatin or cis-diamminedichloroplatinum (II), carboplatin, oxaliplatin, 5-fluorouracil (5-FU), methotrexate, temozolomide, etoposide, and doxorubicin [178]. For instance, upon cell entry, cisplatin is hydrolyzed to an electrophile that attacks nucleophilic centers of the DNA to form interstrand and intrastrand crosslinks, disrupting the structure of the DNA and thereby interfering with DNA replication and transcription [179, 180]. On the other hand, 5-FU and methotrexate impair DNA replication through different mechanisms. These anti-metabolites substitute for the natural nucleotides during replication or promote nucleotide pool imbalances that cause arrest in chromosomal duplication [178, 181-183]. As for temozolomide, this drug acts as an alkylator and reacts with the DNA to form O6 methylated guanine adducts causing cytotoxic and mutagenic outcomes [184, 185]. Finally, agents such as etoposide and doxorubicin act by inhibiting the superhelical relaxation activity of topoisomerases, which leads to protein-DNA adduct formation and DSBs [186-188]. Collectively, the extent of the DNA damage induced by these chemotherapeutic agents overwhelm the cell's DNA repair ability leading to the activation of cell death responses.

Implications of DNA damage in carcinogenesis

DNA damage is implicated in the development of several human diseases including Alzheimer's disease, coronary artery disease, diabetes, chronic obstructive pulmonary disease, and cancer [189, 190]. The relevance of DNA

damage in carcinogenesis became particularly apparent when it was recognized that almost all carcinogenic agents are also mutagenic, causing changes in the DNA sequence [10, 191]. Indeed, studies have shown that the mutation rates in the cancer genome increase when cells are exposed to substantial exogenous DNA damaging agents such as radiation, tobacco smoke, and aflatoxins, which are associated with skin, lung, and liver cancers, respectively [192-197]. These DNA aberrations include substitutions, insertions, deletions of small or large fragments of DNA, genomic amplification, and rearrangements [198, 199]. While some of these aberrations act as passenger mutations that do not directly drive carcinogenesis, others, defined as driver mutations, play a key role in cancer initiation and progression [199-201].

A multitude of acquired alterations have been identified in protein-coding genes that lead to the activation of oncogenes or to the loss of tumor suppressor functions in various types of cancer. One well-characterized example is the set of TP53 mutations, which are extremely widespread in human sporadic cancers, occurring at rates that range from 38%-50% in ovarian, esophageal, colorectal, head and neck, and lung cancers to about 5% in leukemia, sarcoma, malignant melanoma, and cervical cancer [202]. Missense mutations in this gene give rise to mutant p53 proteins that lose their tumor suppressive functions, which drastically disrupt the nature of the p53 pathway, promoting invasion, metastasis and chemoresistance [203]. RB1, another tumor suppressor gene which plays a key role in regulating cell cycle, is also commonly found to be mutated in various cancers, including retinoblastoma, osteosarcoma, and small cell lung cancer. The loss of function of this gene results in increased cell proliferation and a failure in terminal differentiation [204-206]. Cancer development can also be promoted via mutations that activate proto-oncogenes such as secreted growth factors (e.g. PDGF), cell surface tyrosine kinase receptors (e.g. EGFR), signal transduction G-proteins (e.g. RAS), and nuclear transcription factors (e.g. MYC), leading to the stimulation of cell proliferation and expansion of the transformed cell population [207, 208].

Another common class of genomic aberrations in cancer includes chromosomal rearrange-

ments and gene fusions, also resulting in the deregulation of key cellular proteins. One of the most prominent example of reciprocal chromosomal translocation is the t(9;22) Philadelphia translocation observed in chronic myeloid leukemia. This translocation of the proto-oncogene ABL1 located on chromosome 9 to the BCR gene on chromosome 22 results in the BCR-ABL1 fusion gene, which encodes a BCR-ABL1 protein with enhanced tyrosine kinase activity that promotes uncontrolled cell proliferation in the absence of growth factors [209-211]. Another well studied chromosomal translocation is the t(14;18) in follicular lymphoma, which leads to the overexpression of anti-apoptotic protein BCL2, that provides extended survival to B-cells [212, 213]. Although gene fusions are most frequently found in hematological malignancies, they have also been identified in epithelial tumors such as fusion of TMPRSS2 to ERG or ETV1 in prostate cancer, EML4-ALK gene fusion in non-small-cell lung cancer, and RAF kinase pathway gene fusion in gastric and prostate cancer [214]. Needless to say, DSBs are prerequisites for these chromosomal translocations since they facilitate the swapping of chromosomal arms between heterologous chromosomes [215].

In addition to carcinogens acting directing on the DNA sequence and causing mutagenesis, DNA repair processes are also involved in the induction of many permanent DNA sequence changes accountable for oncogenesis. Under normal circumstances, DNA repair processes correct the deleterious DNA lesions thereby suppressing mutagenesis. However, when DNA repair mechanisms are defective, genome instability arises, increasing mutation rates and leading to cellular transformation [216-218]. Inhibitions of proteins involved in DNA repair pathways have been linked to increased risks of various cancers. For instance, hereditary non-polyposis colon cancer is caused by defective MMR [219, 220], and a large proportion of breast and ovarian cancers are caused by mutations in the BRCA1 and BRCA2 genes, which are crucial for the process of DSB repair by HR [221-223]. Other inherited human diseases of DNA repair with cancer susceptibility syndromes include Xeroderma pigmentosum, Ataxia-telangiectasia, Bloom's and Werner's syndromes, and Li-Fraumeni-syndrome [8].

According to the multistep model of cancer development, a lifetime exposure to endogenous and exogenous DNA damaging agents accounts for the progressive accumulation of driver mutations that give rise to a clonal cell population with an advantage in proliferation [224, 225]. Indeed, unlike the non-cancerous somatic cells where genomic integrity is well maintained and cell divisions are strictly controlled, the pre-cancerous cells are prone to a high frequency of genomic changes and alterations due to defects in the regulation of surveillance mechanisms, as well as in the DNA damage checkpoint, DNA repair machinery and mitotic checkpoint pathways [226]. This process, defined as genomic instability, is an enabling characteristic and a driving force of tumorigenesis [227, 228]. Ranging from single nucleotide changes to gross chromosomal alterations, genomic instability is classified into 3 types based on the level of disruption. Nucleotide instability is the increased frequency of a single or a few nucleotide changes (i.e., insertions, deletions, and substitutions); microsatellite instability includes deletions or expansion of short nucleotide repeats called microsatellites; and the most prominent form of genomic instability, chromosomal instability, is characterized by chromosomal abnormalities such as aneuploidy, amplifications, deletions, translocations, and inversions [229, 230].

As mentioned earlier, in hereditary cancers or cancer-predisposing syndromes, including hereditary breast and ovarian cancer, hereditary non-polyposis colon cancer, xeroderma pigmentosum, and MYH-associated polyposis, genomic instability is caused by mutations in DNA repair genes, supporting the mutator phenotype hypothesis [231]. The latter is based on the idea that genomic instability, present in pre-cancerous cells due to mutations in caretaker genes that maintain genomic stability, drives tumorigenesis by increasing the rate of spontaneous mutations [232-234]. On the other hand, genomic instability in sporadic cancers is supported by the oncogene-induced DNA replication stress model in which mutations in oncogenes, checkpoint regulating genes, and tumor suppressors that drive proliferation are responsible for DNA replication stress causing DNA damage and genomic instability in the early cancer stages [235-237]. In any case, unrepaired DNA damage therefore plays a cul-

pril role in cancer development and aggressiveness due to the detrimental consequences of genetic alterations and genomic instability. In the next section, we discuss how the DNA damage response mechanisms activated by DNA lesions are exploited by oncogenic DNA viruses to promote viral integration and cause carcinogenesis.

Role of DNA damage in DNA oncovirus integration and carcinogenesis

Approximately 20%-25% of all human cancers is caused by DNA oncogenic viruses such as HBV, MCV, and HPV [238]. However, infection with these oncogenic viruses does not necessarily cause cancer development. In fact, progression to cancer rarely occurs following infection with an oncogenic virus [239, 240]. Several mechanisms underlying the ability of DNA oncogenic viruses to cause cellular transformation have been reported, with unrepaired DNA damage being the most common and overlapping feature of these oncoviruses to promote tumor development [12, 241]. During viral infections, the host cells generally activate their surveillance mechanisms to detect and repair DNA damage in order to maintain genomic integrity. Many viruses also stimulate DNA damage signaling pathways, either directly by virus infection itself or indirectly via the expression of viral proteins, to ensure an S-phase-like replication environment, preventing apoptosis and promoting episomal maintenance [242]. However, when DNA damage accumulates in the host genome and the activated DNA damage repair system is not sufficient to repair the lesions, one side-effect is the integration of the viral episome into the host genome, which can trigger cancer development in the infected cells.

Integration of the viral genome is a crucial event in the process of malignant transformation for several oncogenic viruses. For example, integration of the HBV episome into the genome of hepatocytes has been reported in over 85%-90% of HBV-related hepatocellular carcinoma cases [243-245]. HBV integration leads to overexpression of cellular cancer-related genes, such as telomerase reverse transcriptase (TERT), mixed-lineage leukemia 4 (MLL4), and CCNE1 encoding cyclin E1 [246]. Furthermore, integrated HBV sequences encoding HBx and/

or truncated envelope pre-S2/S proteins induce genomic instability and cell cycle deregulation by interfering with NER, repressing p53-mediated gene transcription and inactivating p53-dependent tumor suppression, as well as transactivating several cellular genes and signaling pathways linked to carcinogenesis [247-252]. Overall, HBV integration promotes further genetic alterations such as chromosomal deletions, translocations, fusion of transcripts and amplification of DNA, which lead to activation of oncogenes and depletion of tumor suppressor genes, promoting the development of hepatocellular carcinoma [253, 254].

While HBV integration contributes to carcinogenesis by stimulating both cellular and viral responses, integration of HPV into the host genome solely activates viral mechanisms that promote malignant transformation. Integration of HPV into the host genome typically results in the disruption and loss of the viral negative regulator E2, allowing persistent over-expression of the two viral oncoproteins, E6 and E7 [255-258]. The E6 oncoprotein causes evasion of apoptosis and perturbation of cell cycle control by forming a complex with p53 and targeting it to proteasomal degradation. On the other hand, the E7 oncoprotein stimulates unrestrained replication and cell division by binding to and stimulating the degradation of Rb, leading to the inappropriate release of the E2F transcription factor. Therefore, when these viral oncoproteins are over-expressed following viral integration, the HPV-infected cells undergo uncontrolled cellular proliferation and survival, and consequently develop HPV-induced malignancies [259-261]. It is estimated that about 90% of HPV-positive cervical cancer cases contain HPV integrated into the host genome, supporting the idea that development of cervical cancer in HPV-infected women is tightly linked to the integration status of the virus [262-264]. The frequency of HPV integration in other anogenital cancers is not as well documented, with one study reporting integrated HPV in nearly 80% of anal cancer cases [265]. In the case of HPV-positive head and neck carcinomas, viral integration has been detected at lower rates, with many tumors having either episomal or mixed episomal and integrated viral DNA [266-268].

As for MCV, integration of this viral episome into the human genome has been noted in

70%-80% of Merkel cell carcinoma tumors [269, 270]. While the exact role of MCV integration in Merkel cell carcinoma development requires further study, it has been documented that the integrated viral genome almost always contains mutations that truncate the C-terminal DNA binding and helicase domains of large tumor (T) antigen, preventing auto-activation of integrated virus replication, which would be detrimental for cell survival [271-273].

Although the mechanism of these viral integrations has not been well defined, none of these DNA oncoviruses encode genes that produce integrase enzymatic activity proteins similar to those encoded by the human immunodeficiency virus [274]. Instead, the integrative process of these oncogenic viruses is thought to be linked to the extent of DNA damage existing in the host cells. According to this model, viral integration requires DSBs in both the host DNA and in the circular viral episome, following which the recruitment of DNA damage repair complexes ensures the accessibility of ligases that can reconnect the recombined host and viral sequences, creating the perfect microenvironment for viral integration [12, 275]. While DSBs can be directly caused by exogenous DNA damaging agents and IR as discussed earlier, spontaneous DSBs also occur at a rate of 1 DSB per 10^8 bp during normal cellular processes [276]. Furthermore, it has been reported that about 1% of single strand DNA lesions such as SSBs, AP sites, oxidation products 8-oxoG and TG, and alkylation products, are converted to 50 DSBs per cell per cell cycle during the S phase (a rate of 1 DSB per 10^8 bp) [277]. Indeed, if left unresolved, SSBs cause the collapse of a replication fork, leading to DSB formation; while unrepaired base damages in the template strand cause stalling of replication fork, leading to the formation of nicks and gaps in DNA that generate DSBs (reviewed in [116]). Consequently, these simultaneous breaks in the phosphate backbones of the two complementary DNA strands serve as integration sites for oncogenic DNA viruses (**Figure 1**). In support of this hypothesis, environmental conditions known to cause DNA damage have been epidemiologically associated with increased incidence of viral-induced carcinogenesis. For instance, exposure to UV and possibly ionizing radiation is a risk factor for MCV-induced Merkel cell carcinoma [278-280]. In the case of HBV-related hepatocellular carcinoma, environ-

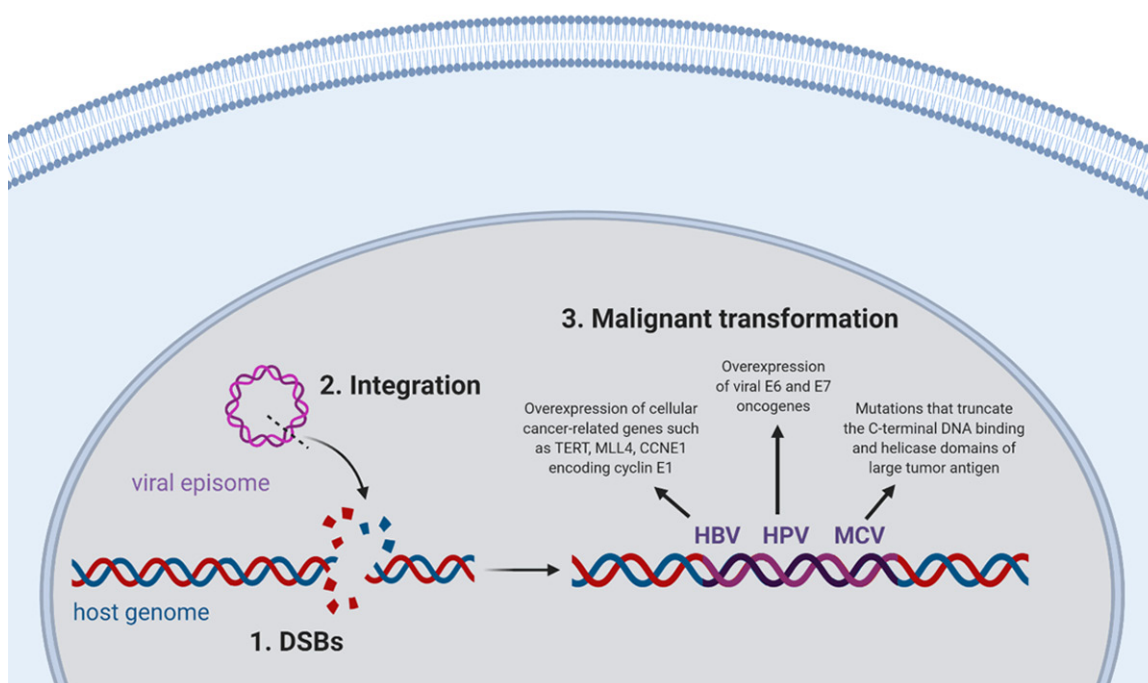


Figure 1. DNA lesions serve as integration sites for oncogenic DNA viruses and promote malignant transformation of the infected cells. Created with BioRender.com.

mental risk factors include aflatoxin B1 exposure, alcohol consumption and smoking [281-286]. As for HPV-mediated malignancies, smoking, long term use of oral contraceptives, high parity, inflammation, and co-infections with STD-associated pathogens *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are considered as non-viral risk factors [287-294]. Several publications have also reported increased oxidative stress and subsequent DNA damage in patients with cervical carcinoma compared to normal population (reviewed in [295]). In addition to these observational and epidemiological studies, some pieces of evidence have also mechanistically linked DNA damage to a higher integration frequency of these oncogenic DNA viruses. For example, the integration frequency of HBV into the host genome has been shown to be increased in the presence of DNA strand breaks induced by oxidative stress [296]. In the case of HPV, Winder et al. (2007) have demonstrated that generation of DSBs due to Ku70 depletion in cervical keratinocyte cell line W12 containing HPV16 episomes results in the integration of viral DNA into the host genome [297]. Our lab has also shown that chronic oxidative stress, induced either by the exogenous agent L-Buthionine-sulfoximine or by the HPV E6* protein, increas-

es the frequency of integration of HPV16 into the genome of cervical keratinocytes [275]. Furthermore, the activity of DNA-dependent protein kinase, an important enzyme involved in DSB repair via the NHEJ pathway, has been found to be significantly lower in patients with cervical cancer, compared to a healthy population [298]. It was recently demonstrated that this disruption of the NHEJ pathway is mediated by the HPV16 E7 oncoprotein and often results in a reciprocal increase in microhomology-mediated end-joining [299]. Supporting this observation, integration breakpoints in cervical and oropharyngeal cancers have been found to be enriched with micro-homologous sequence between the HPV and human genomes, indicating the involvement of microhomology-mediated DNA repair pathways in the process of HPV integration [266, 300]. Collectively, these data support the idea that DNA lesions can serve as sites for viral integration and that inducing DNA damage dramatically increases viral integration frequency.

Conclusions

To summarize, the DNA molecule is subject to continuous damage from a combination of endogenous and exogenous sources. Endoge-

nous DNA lesions are caused by cellular metabolic and physiological processes such as oxidation, hydrolysis, alkylation, and polymerase incorporation errors, whereas exogenous sources of DNA damage include exposure to environmental factors such as IR, UV radiation, chemical agents (aromatic amines, alkylating agents, PAHs, reactive electrophiles, aflatoxins) as well as chemotherapeutic agents. When left unrepaired, DNA damage accumulates in the cells and gives rise to mutations that change the function of important genes (i.e. activation of oncogenes, loss of tumor suppressor functions), or causes chromosomal rearrangements and gene fusions that also result in the deregulation of key cellular proteins. Progressive acquisition of such genetic mutations promotes uncontrolled cell proliferation and evasion of cell death, and hence plays a key role in cancer initiation and progression. Another less-studied consequence of DNA damage accumulating in the host genome is the integration of oncogenic DNA viruses. This critical step of malignant transformation by HBV, MCV and HPV is thought to be particularly facilitated by DSBs in both viral and host genome. Therefore, the impact of DNA damage on carcinogenesis is magnified in the case of these oncoviruses via the additional effect of increasing integration frequency.

In this paper, we also reviewed the limited data connecting DNA damage and repair mechanisms with viral oncogenesis through viral integration. As discussed, several epidemiological pieces of evidence point in support of the idea that DNA damaging agents are risk factors for viral integration and subsequent carcinogenesis, yet mechanistically only a few studies have examined the connection of these DNA damaging agents with viral oncogenesis. Therefore, a critical evaluation should be undertaken to further assess the etiology of virus-mediated carcinogenesis and identify the DNA damage pathways involved in the progression from viral infection to cancer development. In particular, the role of these non-viral factors in viral integration needs to be more clearly elucidated, with the ultimate goal of reducing or eradicating these viral-mediated malignancies that account for about 20% of human cancers worldwide. Indeed, demonstrating that a certain DNA damaging agent increases the likelihood of viral-host integration and magnifies the process of carcinogenesis will enable the develop-

ment of both preventative and therapeutic strategies designed specifically to intercept the critical step of malignant transformation by the oncogenic DNA viruses. For instance, the current epidemiological data support the implementation of precautionary measures such as HBV vaccination programs in regions with high AFB1 exposure as well as abstinence from smoking and alcohol to prevent hepatocellular carcinoma, or cessation of smoking and limitation of oral contraceptive for HPV management. More importantly, research on the molecular mechanisms involved in viral integration will allow the development of more effective treatment approaches to eradicate virus-based carcinogenesis. Of particular interest, molecules such as poly(ADP-ribose) polymerase-1 (PARP-1) that protect DNA strand breaks and act as anti-recombinogenic factors need to be the focus of future studies, since these guardians of genomic integrity have the potential to prevent viral integration [296].

Disclosure of conflict of interest

None.

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