



Unboxing the molecular modalities of mutagens in cancer

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Abstract

The etiology of the majority of human cancers is associated with a myriad of environmental causes, including physical, chemical, and biological factors. DNA damage induced by such mutagens is the initial step in the process of carcinogenesis resulting in the accumulation of mutations. Mutational events are considered the major triggers for introducing genetic and epigenetic insults such as DNA crosslinks, single- and double-strand DNA breaks, formation of DNA adducts, mismatched bases, modification in histones, DNA methylation, and microRNA alterations. However, DNA repair mechanisms are devoted to protect the DNA to ensure genetic stability, any aberrations in these calibrated mechanisms provoke cancer occurrence. Comprehensive knowledge of the type of mutagens and carcinogens and the influence of these agents in DNA damage and cancer induction is crucial to develop rational anticancer strategies. This review delineated the molecular mechanism of DNA damage and the repair pathways to provide a deep understanding of the molecular basis of mutagenicity and carcinogenicity. A relationship between DNA adduct formation and cancer incidence has also been summarized. The mechanistic basis of inflammatory response and oxidative damage triggered by mutagens in tumorigenesis has also been highlighted. We elucidated the interesting interplay between DNA damage response and immune system mechanisms. We addressed the current understanding of DNA repair targeted therapies and DNA damaging chemotherapeutic agents for cancer treatment and discussed how antiviral agents, anti-inflammatory drugs, and immunotherapeutic agents combined with traditional approaches lay the foundations for future cancer therapies.

Keywords Mutation · DNA damage · DNA repair mechanism · Inflammation · Immunotherapy

Introduction

Genomic integrity is an essentiality that needs to be maintained and assured. Alterations arising from various genotoxic factors like stress induced due to environmental agents and toxins, exposure to ionizing radiations, DNA replicative errors, and various endogenous and exogenous metabolites thus hamper the cellular deoxyribonucleic acid (DNA). As these mutagenic factors affect the molecular signature of DNA, they exert different mutational signatures, which helps predict the extent of damage caused to the complex cellular machinery comprising DNA. These environmental mutagens also affect

at the level of metabolism by interrupting the metabolites involved in maintaining the state of various enzymes (for example, cyclooxygenases and oxygenase) involved in commanding multiple pathways (Volkova et al. 2020). Ubiquitination plays a prominent role in cancer. Evident studies suggest that ubiquitin E3 ligases such as the expression murine double minute 2 (MDM2) are highly upregulated in various cancers that affect various downstream targets like p53. These mutagens distort the regulatory machinery of these ligases, thereby causing progression in cancer (Gupta et al. 2019). The extent of the damage caused depends on the mutagens' structural and molecular capabilities to which the DNA is exposed. Studies predict that these environmental mutagens are highly damaging as these can lead to carcinogenesis and aging of the affected cells. Therefore, this level of damage is caused via chromosomal instability, modification in the sequence of bases of DNA, and aneuploidy (Karthika et al. 2021). Mutagens that cause this variable damage can be physical, biological, and chemical in nature (Temko et al. 2018). Physical mutagens such as lead, arsenic, cadmium, and mercury are known to be associated with cancer and are potent carcinogens. These

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mutagens bind and cause mutation in the sequence of DNA bases either by interacting with proteins that bind to the DNA or by halting the repair machinery of DNA, thereby increasing the level of mutations and prompting carcinomas of various origin (Kabir et al. 2021). Evident studies suggest cadmium's role in inducing non-small cell lung carcinomas (NSCLCs), prostate, and cancers of biliary regions (Hartwig 2013). Exposure to radiations of ionizing nature such as UV and gamma also causes denaturation that further leads to spontaneous mutagenesis (Toxicology 1992). These mutagens increase reactive oxygen species (ROS) aggregation level that binds with the nucleic acid, enhances apoptosis and oxidative stress, causing tumor loading and unclear abnormal cellular check.

Similarly, various classes of chemical mutagens (alkylating agents, DNA intercalating agents, and deaminating agents) such as melphalan, benzidine, and diethylstilbestrol mediate base-analog and cause pyrimidines to shift, leading to mutagenesis in healthy cells (Weber et al. 2002). Studies also define the role of various infectious mutagens (bacteria and virus) that also interferes with the biological integrity of cells. Viruses of various modalities like the Epstein-Barr virus, hepatitis B, and C elevate the cellular damage and are known to be linked with carcinogenesis (Li et al. 2004). Another interesting character that comes into foreplay is hypoxia, being heterogeneous in nature, causes a metabolic shift in DNA stability by being linked with ROS generation causing oxidative stress and death of cells. Hypoxia-inducible factor (HIF-1 α), a major transcription factor in hypoxia, is also somewhere known to be linked to promoting carcinogenesis in healthy cells (Jun et al. 2017; Kaplan and Glazer 2020). Epigenetic and genetic mechanisms are also known to be associated with the growth and development of various tumors (Rahman et al. 2021). Mutagens that interfere with the pathways associate with these mechanisms, such as differentiation, histone modifications, acetylation, methylation, etc., also degrades the DNA quality, causing cancer. Mutagenic agents of this class are also known to be activation-dependent and activation-independent mutagens. Examples of these DNA-damaging carcinogens include mycotoxins, polycyclic aromatic hydrocarbons, forms DNA adducts. Studies that govern the role of mutagens being the associator in the formation of DNA adducts are extensively described (Arlt et al. 2005; Totsuka et al. 2021). Also, how these DNA adducts are identified using sophisticated molecular techniques such as gas chromatography, liquid chromatography/mass spectroscopy (LC/MS), and fluorescent methods in the measurement of DNA adducts is an important concept, preventing adduct formation and cellular damage. Many studies have explored the therapeutic potential of natural compounds and phytochemical extracts in reducing the countereffects of these mutagens in various carcinomas (Grover et al. 2021).

Evident studies prescribe the role of environmental mutagens (endogenous and exogenous) in mediating inflammation-associated pathways. As these pathways help in mediating DNA damage and play a key role when talking about carcinogenesis, it is important to explore these associations (Bhattacharya et al. 2021; Piotrowski et al. 2020). Downregulation elements in these signaling like the nuclear factor- κ B (NF- κ B), signal transducer and activator of transcription 1 (STAT1), interferon regulatory factor 3 (IRF 3), and activation of caspases and bridging with mutagens opens up a window how these mutagens guide inflammation, ultimately leading to cancer, the chunk of which is described in detail in this review (Preventive 2018). The release of various inflammatory cytokines like the IL-2, IL-10, and TNF- α and their secretions influence DNA-damage response and activation of pathways such as the JNK/STAT1, which can act as a therapeutic possibility targeting inflammation in cancer (Sandhir et al. 2017; Fadriqela et al. 2021). In order to achieve stable, and functional DNA integrity, a certain DNA-repair mechanism comes into action when struck by the effect of any exogenous and endogenous mutagens. These DNA-repair mechanisms include single-strand break repair (SSB) comprising the base-excision repair (BER), nucleotide-excision repair (NER), and mismatch repair. For more severe damage (double-stranded DNA break), homologous recombination (HR) and non-homologous end-joining (NHEJ) commands the repair machinery that is affected by these environmental mutagens (Chatterjee and Walker 2017). Deformity in the repair mechanism affects the cellular machinery that ultimately leads to the formation of an abnormal mass of cells, causing cancer. Therefore, targeting these repair mechanisms can be an asset to how these mutagens affect the cellular DNA and in the prevention of carcinomas. Also, it is necessary to explore inhibitors that could potentially target these damages caused by various environmental mutagens, as an early detection and prevention can be a game-changer when talking about how these environmental modulators impact the DNA and lead to the establishment of a deadly disease so-called cancer.

Environmental mutagens as DNA damage activators enhancing carcinogenesis

Any environmental substance that causes a mutation is known as a mutagen, and these agents are called mutagenic agents. Cancer-causing mutagens are known to be carcinogens, but not all mutants are necessarily carcinogenic in nature (Griffiths et al. 2000; Errol 2001). Every single mutant knows to characteristic mutational signatures (combinations of mutation types arising from specific mutagenesis processes such as DNA replication infidelity, exogenous and endogenous genotoxins exposures, defective DNA repair pathways, and

DNA enzymatic editing) (Kaoru 2016). Some mutation is known as “spontaneous mutations” due to spontaneous hydrolysis, DNA replication errors, repair, and recombination (Ripley 2013). Some mutants are known as promutagens that exert their effect through their metabolites, and conversion of these metabolites into carcinogenesis depends on the metabolic process of an organism, for example, through the activity of the cytochrome P450 system and other oxygenase such as cyclooxygenase (Kim and Guengerich 2005; Martín-Sanz et al. 2017). Different mutagens act differently on DNA, for example, some mutagens induce chromosomal instability, including chromosomal breakages and rearrangement of the chromosomes such as translocation, deletion, and inversion (Mishima 2017). In the same way, some mutagens modify DNA sequence involving the substitution of nucleotide base-pairs, insertions and deletions of one or more nucleotides in DNA sequences and others lead to aneuploidy (Mandrioli et al. 2016). The complicity of environmental mutagens (DNA damaging agents) in biological processes and how it is linked to cancer has been shown in Figure 1. The role of mutagens has also been briefly described below.

Physical mutagens triggered mutagenesis

Environmental agents (physical, chemicals, radiation, and biological) can be mutagens (mainly that alter DNA) or carcinogens (cancer-causing substances). The steps involved for a mutagen to become a carcinogen to cause cancer involve the metabolic activation, reaction with DNA to form DNA adduct, and then DNA replication of this adduct, subsequently resulting in a mutation. This mutation (in a cancerous gene) results in enhanced growth potential and ultimately induces tumor. The physical mutants are present in our surroundings, possessing mutational signatures that alter the genetic information or change an organism’s DNA sequence. These primarily include heavy metals and heat. In the current scenario, many heavy metals are known to be contagious to well-being, and studies suggest some acts as potential carcinogens too. The metals can either endogenously or exogenously damage the DNA by producing ROS, thereby impairing the repair mechanisms. Additionally, comprehensive studies have revealed that heavy metals can cause various diseases like cardiovascular diseases, autoimmune disorders, neurodegenerative disorders, etc. The damage caused by arsenic (As), lead (Pb), cadmium (Cd), chromium (Cr), and mercury (Hg) has a long history as a carcinogen. There are multiple mechanisms by which these metals can induce carcinogenesis, as the exposure of these heavy metals directly or indirectly disrupts the intracellular processes. And thus, these processes have potential candidature for acting as markers of heavy metal-induced carcinogenesis.

As is known to be one of the most common mutagenic agents that is also a potential class I human carcinogen.

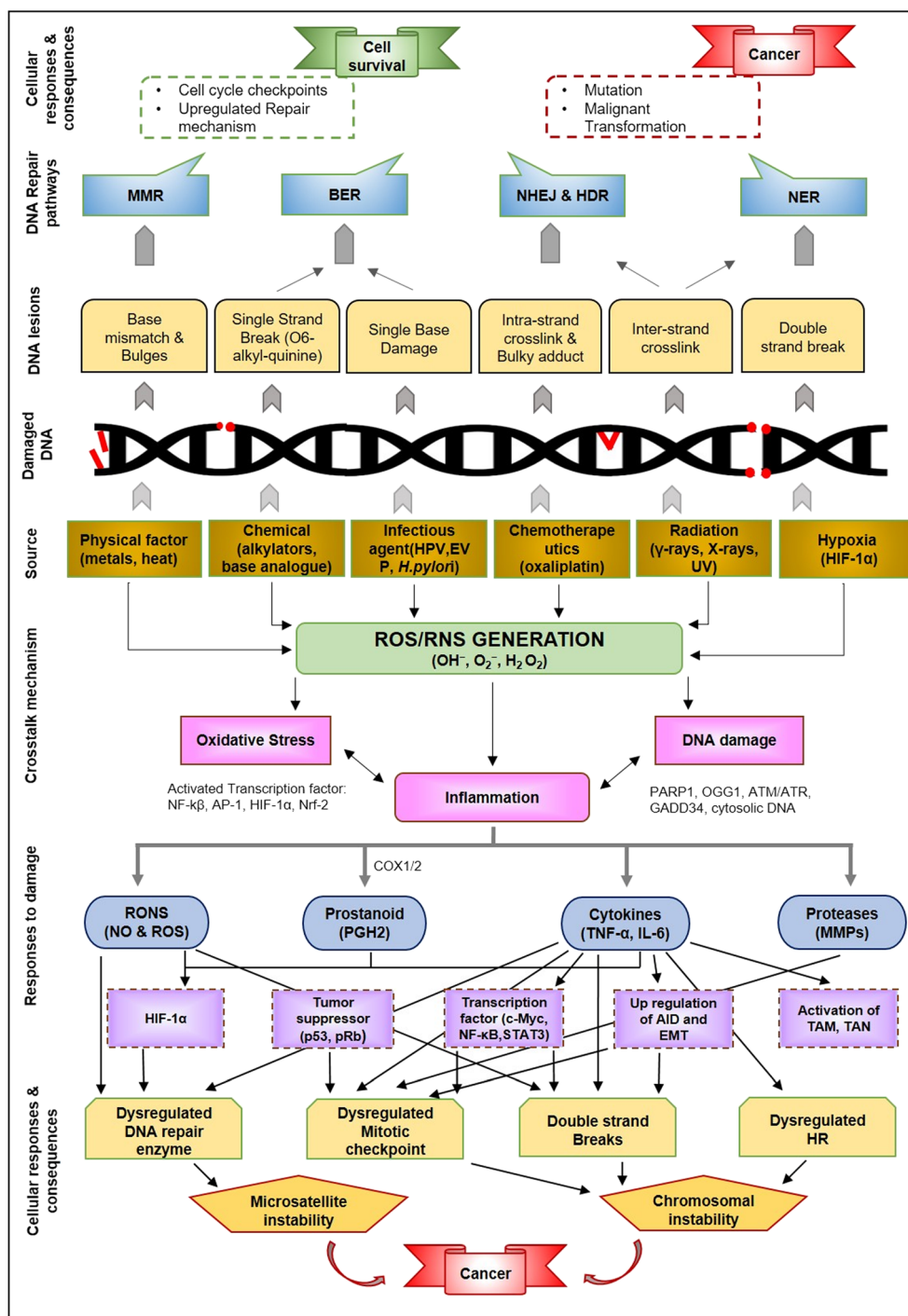
There is an enormous collection of writing supporting As-related carcinogenesis (Vega et al. 1995; Salazar et al. 2010; Tokar et al. 2010). Being a toxic semi-metal, As exists in mainly inorganic form as arsenate and arsenide in nature. These inorganic forms are highly hazardous to health as they can cause skin, lung, and liver cancers (D’Souza and Peretiako 2002; Martinez et al. 2011). Also, As residues interact with DNA-binding proteins and disrupt the DNA repair machinery and increase the risk of carcinogenesis. The studies have also stated that exposure to As alone is not satisfactory enough to cause cancer, it just acts as a co-carcinogen whose effect is enhanced when combined with the other mutagenic agents like UV radiations or Benzo(a)pyrene diol epoxide (BPDE), which give rise to high genomic instabilities and finally results in tumorigenesis (Rossman et al. 2004), which is beneficial for the evaluation of its bioeffect. The comprehensive studies suggest that As (III) and BPDE synergistically lead to genotoxicity, DNA strand break damage, and causes carcinogenesis. The plausible mechanism of action is by inhibiting As metal methylation, in return As(III) inhibits nucleotide excision repair (NER) of the DNA adduct damage caused by BPDE (Li et al. 2019).

Also, occupational exposure to another heavy metal, Cd, is concerned with toxicity and carcinogenesis as evidence suggests it to be a prime suspect causing lung cancer (Nawrot et al. 2006). However, exposure to cadmium is equally responsible for causing tumors in other organs like the kidney, breast, and prostate (Nordberg et al. 1975; Dudley et al. 1985; Lauwerys and Bernard 1986; Itoh et al. 2014). In general, the cadmium-induced carcinogenicity triggers the proteins involved in DNA damage and results in cellular growth deregulation and apoptotic resistance of cells (Hu et al. 2002).

On the other hand, lung cancer is also diagnosed in people working in the chromate-producing industry, indicating that Cr is also a primary cause (Langård and Vigander 1983). The Cr dust is highly insoluble in water; after entering the body, it settles down in blood vessels and produces ROS. These ROS then bind with DNA, causes cellular damage, further inducing apoptosis, oxidative stress, and cancer in the lungs and kidneys. In addition to above mentioned, other prevailing mutagenic metals known to provoke carcinogenesis are listed in Table 2, along with the cancer they cause and current medications used.

The shifting temperature has been quite long known to cause mutations in various organisms (Waldvogel and Pfenninger 2020). These mutations are caused by a raised weather that does not directly affect the DNA but results from perturbations of the enzymes involved in DNA synthesis. The heating of DNA over 95 °C leads to denaturation and breakage of phosphodiester bonds, while heating to 36 °C is known to cause spontaneous mutagenesis. From the studies, it has been found that the rate of heat-induced mutation in T4 is nearly 4×10^{-8} at 37° per G-C base pair/day. While for the

Fig. 1 Model for environmental risk factor, DNA damage, and its response in biological processes linked to cancer: Repetitive exposure of cells to intrinsic and extrinsic carcinogens may result in accumulation of free radicals such as ROS, which leads to oxidative stress and DNA damage and together with all results into inflammation. These generate various growth factors (VEGF), cytokines (TGF- β , TNF- α , IL-6, etc.), transcription factors (c-Myc, NF- κ B, STAT3), HIF-1 α . Elevation ROS upregulates the expression of MMPs through TGF β . Furthermore, ROS also mediates the expression of vimentin and VEGF, which increases EMT (promotes cancer cell migration) and angiogenesis, respectively. DNA damaging agents also generate a variety of lesions, such as mismatched nucleotides, base lesions, bulky (helix-distorting) adducts, SSBs, or DSBs, which causes mutations that have specific cellular consequences, including transformation or cell death. Cellular events lead to genomic or microsatellite instability, which causes cancer. The dysregulated DNA repair mechanism is unable to recognize DNA lesions and which may subsequently lead to carcinogenesis. AID, activation-induced cytidine deaminase



human genomes, this value accounts for 100 per diploid cell/day (Siddiqui and Khan 1999). Thus, all the evidence advocates that heat can also act as a common physical mutagen.

Congeneric series of chemical mutagens

Percival Pott, in 1775, was the first one to report a case of occupational cancer caused by the mutagens present in a work environment. He observed that prolonged exposure to

chimney sweeps was a major contributory factor towards the development of scrotal cancer in men. These sweeps contain potential DNA-damaging agents, polycyclic aromatic hydrocarbons, which cause mutations and lead to cancer development (Androustos 2006). Thus, chemicals that alter the DNA are known as chemical mutagens. These include alkylating agents, hydroxylation agents, deaminating agents, intercalating agents, base analogs, etc. Most of these are mutagens, and some of them even act as potential carcinogens.

Interestingly, International Agency for Research on Cancer (IARC) has listed 88 chemical agents as human carcinogens based on animal bioassays (generally conducted in rats and mice). These animals were exposed to high doses of these agents, typically for two years. These agents include organic compounds (Naphthalene, 4-Aminobiphenyl, Benzidine, Chlornaphazine, Diethylstilbestrol, Melphalan, and many others), hormones (Estradiol), fibers (Asbestos, Erionite), components of soot, tar, etc. (Little et al. 2009; Botelho et al. 2014). These mutagens are present abundantly in our surroundings, like in tobacco smoke, air pollution, and even are generated by processes involving the peroxidation of lipids. Mostly these chemical agents are potential carcinogens that react with bases of the DNA to form mutagenic adducts and are used as a biomarker for diseases related to neurodegeneration, metal storage disorders, and may even cause inflammation or cancer, etc. (Sanchez et al. 2021a; Kaur et al. 2021). Even alcohol consumption is a prime factor related to inducing carcinomas of the head, neck as well as esophagus. The mechanism of alcohol-induced cancer is not known, but the aldehyde products of alcohol oxidation interfere with DNA, resulting in adduct formation, which can lead to several mutations. Importantly, past studies have shown that aldehyde-derived DNA adducts like N^2 -ethyldeoxyguanosine, N^6 -ethyldeoxyadenosine, and N^4 -ethyldeoxycytidine are known to have genotoxic effects in humans (Guidolin et al. 2021). Thus, performing high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) for the detection of exocyclic DNA adducts confirms about the DNA damage caused due to alcohol exposures play a critical role in cancer etiology. These chemicals, their mechanism of action, and cancer they induce have been summarized in Table 2.

Generally, the chemical mutagens are classified into different categories (base analogs, intercalators, alkylating agents, etc.) based on their mode of action. Base analog mutagens are the chemicals that resemble normal bases structurally; they take part in DNA replication as these are misread by repair mechanisms as normal bases only. The 5-bromo-deoxyuridine (5BU), a synthetically synthesized compound that resembles the thymine, is the most studied base analog whose keto form (T mimic) and pairs with “A” typically (CASPARI et al. 1965). This potent mutagen is capable enough to cause point mutations resulting in deleterious alterations in genetic information. Certain other chemicals such as Azidothymidine (AZT) and 2-aminopurine (2-AP) also belong to the category of base analogs (Ma et al. 2017.; Persing et al. 1981), and each of these chemicals mutagenizes over time because of their resemblance with the normal bases. After undergoing multiple rounds of replication, these mutations are stabilized.

The chemical mutagens also comprise influential mutagens known as alkylating agents, deaminating agents, and DNA intercalating agents. The alkylators such as ethyl methane sulfonate (EMS) and nitrosoguanidine (NTG, NG, MNNG) are

agents which cause alkylation of DNA by reacting with the nucleotide bases. These mutagens are inclined towards G-rich regions and react to form modified “G” residues, thereby undergoes depurination. Thus, the alkylation of DNA leads to many reactions like the formation of unstable triesters, which release the alkyl group and hinders the DNA replication machinery. Even these phosphate triesters, when hydrolyzed, lead to the breakage of the DNA backbone (Jones et al. 2010). Many other chemicals also act as mutagens like hydroxylamine, sodium azide, and nitrous acid, which cause oxidative deamination and cause fatal base pairing. Unlike other mutagens, nitrous acid directly modifies a base into a miscoding form and converts adenine to hypoxanthine, cytosine to uracil, and finally guanine to xanthine (Hartman et al. 1994). Among others, DNA-intercalating agents include acridine orange, ethidium bromide (EtBr), and daunorubicin which lead to distort the DNA helix and cause frameshift mutations either by adding or deleting certain bases. These compounds seemingly mutagenize by intercalating between bases present adjacent to one other, conceivably making repair systems reflect as if there is an alternative base at that position. The heterocyclic nitrogen mustard gas is a well-known example of it. Even some dyes like acridine orange, proflavine, and acriflavine have structures similar to those of purines and pyrimidines, and thus, they insert themselves in DNA. These intercalating agents distort DNA structure, lead to wrong base pairing, and are associated with single nucleotide-pair insertions, frameshift mutation (deletions) (Hoffmann et al. 2003) soot. In contrast, some studies have shown the pharmacological effect of Proflavin as it inhibits human osteosarcoma via apoptosis and autophagy (Karthika et al. 2021; Zhang et al. 2015a). Similarly study by Lin et al. showed that Acridine orange exhibits photodamage via disrupting acidic organelles and induces bladder cancer cells death underneath blue light exposure (Lin et al. 2017).

Radiation-induced mutation and DNA damage

The U.S. Environmental Protection Agency (EPA) states that all radionuclides are carcinogens under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA). The carcinogenicity of radiations depends on their type, exposure, and penetration power. There are different types of radiation like (a) ionizing radiation such as X-rays, gamma rays, and alpha particles; (b) ultraviolet radiations (UV) with wavelength above 260 nm; and (c) radioactive decay, such as the decay of ^{14}C incorporated in DNA into nitrogen. In a living cell, radiation can damage proteins, lipoproteins, DNA, carbohydrates, etc., either by directly ionizing or exciting or indirectly by generating highly reactive species by radiolysis of the cellular water. These radiations perpetuate genetic effects, and, thus, the cellular repair system is largely ardent to its well-being. The radiations

are a type of environmental mutagen that leads to immediate changes in a cell's DNA like the ionizing radiation (i.e., X-rays) break DNA sequences; UV rays (mainly UV-B 280–315 nm), penetrate through cellular and nuclear membranes resulting in DNA damage, UV-radiation induced free radical generation, and formation of dimers. ROS leads to damage to lipids, proteins, and cell structure, and DNA, resulting in oxidative stress involved in many cancer (Rastogi et al. 2010).

Broadly, there are two types of ionizing radiation, and one comprises corpuscular rays like alpha, beta, protons, etc. The alpha particles are a type of low penetrating radiation that shall consist of two protons and two neutrons. Whereas the beta particles more penetrating and less ionizing, consisting of electrons or positrons. These beta rays, alpha rays, fast and thermal neutrons are also known to cause chromosomal breakage and gene mutations (Loucas et al. 2013; Roychowdhury and Tah 2013; Yusuff et al. 2015; Kumawat et al. 2019). According to the epidemiological evidence, there are many health risks associated, including cancer risks at several anatomical sites (lungs, bones, liver, etc.) with radionuclides emitting these particles (El Ghissassi et al. 2009; Graf et al. 2014). In contrast, the other type of ionizing radiation includes electromagnetic rays like X-rays, gamma rays. The mechanism of action of X-rays and γ rays both are the same as they are penetrable, non-is particulate in nature, thereby causing double-strand breaks (DSBs) in DNA. These DSBs in the DNA lead to either deletion or rearrangement and may become lethal in some cases too, and every DSB possesses the same tendency of inducing a cell transformation, and each transformed cell has the potential to develop into cancer (Kirby-Smith and Daniels 1953). Simultaneously, it has also been observed that sometimes the bases get oxidized due to the ionizing radiations. For instance, guanine (G) gets oxidized to form Oxo G, which can base pair with both A as well as C, and it pairs with A then it causes transversion mutation (GC base pair changes to AT).

Another common mutagen is UV radiation, responsible for transforming healthy cells into cancerous (especially skin cancers) as they inactivate apoptosis (Laikova et al. 2019). These UV radiations excite the DNA molecule and cause crosslinking, single-strand breaks (SSBs), leading to the formation of pyrimidine dimer. Generally, cytosine (C) and thymidine (T) are more vulnerable to UV radiations and form dimers. These dimers distort the helical conformation of the DNA, weaken H-bonds, and inhibit the advancement of the replication fork (Rastogi et al. 2010). Moreover, UV radiation's ability to induce and promote malignant melanoma was conjointly shown in many animal models. It also alters cytokines such as TNF- α and interleukins (ILs), which indirectly affects matrix metalloproteinases (MMPs) synthesis, thereby promoting melanoma metastasis and invasion (Anna et al. 2007).

The radioactive materials after undergoing the decay process also induce mutagenesis, for instance, Sulfur-35 decays into Chlorine, Strontium-90 decays into Yttrium-90, and Barium-140 decays into Lanthanum-140, all of them interact and bind with DNA and results in DNA damage as well as genetic mutations (Chen 2013). Also, some studies suggest that iodine-131 used to treat thyroid cancer may lead to leukemia (Carhill and Vassilopoulou-Sellin 2012; Gilabert and Prebet 2012; Alsaud et al. 2020). Thus, in different ways, radiations are known to cause mutations depending upon their penetration power, dosage, and energy it possesses.

Infectious agents mediated mutagenesis

Some mutagens of biological origin are also known to cause mutations. These agents are sources of DNA from elements like transposons, bacteria, parasites, and viruses. The transposons are commonly known as jumping genes. These are non-coding sequences of DNA that relocate and replicate autonomously. The insertion into a DNA sequence of transposons can disrupt traditional gene functions (Woodford and Ellington 2007). The transposable elements can act either as oncogenic factors (e.g., HRas proto-oncogene, Myc oncogene, etc.) leading to genomic instability (deletions, insertions, Chromosomal mutations), or interfere with transcription factors and non-coding RNAs whose dysregulation further leads to carcinogenesis (Anwar et al. 2017). Lately, scientists have found on comparing adenomatous polyposis coli tumor suppressor (APC) genes in healthy and colon cancer suffering cells on later consists of transposes. This further testifies the fact that transposes in somatic cells in mammals have some role in the development of colorectal cancer (Miki et al. 1992; Chenmala et al. 2021). Viruses are a common infectious agent that can induce mutagenesis as they can insert their DNA into the host genome and disrupt the gene functionality. Once inside the host, viruses use the host machinery to replicate, translate, and express their viral proteins. These viral mutations can be point mutations, including base substitutions and deletions and insertions (Shapiro et al. 1984). Some viruses are also known to cause cancers, and these are known as oncogenic viruses. These viruses' mechanism of action is that they insert a viral oncogenic gene into the host, which further augments already existing proto-oncogene, which becomes oncogene. Examples of such viruses include Hepatitis B, Hepatitis C, Kaposi sarcoma-associated herpesvirus (KSHV), Epstein-Barr virus, Human papillomavirus, etc. (Zur Hausen 1991). The viruses and their mechanism of action have been explained in detail further in this paper.

A few microscopic organisms like the bacteria *Helicobacter pylori* (*H. pylori*) can cause inflammation during which oxidative species are released, thereby leading to DNA harm and lessening the DNA repair system's productivity to a high mutational rate. *H. pylori* is a human carcinogen known

to cause mutations in the gastric mucosa and finally leading to cancer (Rahman et al. 2019; Sheh et al. 2010). Some studies suggest *H. pylori* infection causes prolonged inflammation, and it is evident from the overexpression of cytokine (IL-1) in the stomach transgenic mice (Tu et al. 2008). These organisms later advance into erratic gastric inflammation and cancer as the inflammatory response may have predisposed cells in the stomach lining to become cancerous. The augmented cell turnover consequential due to the ongoing cellular damage possibly will increase the likability of harmful mutations. The other bacteria associated with causing cancer include *Salmonella typhi* (*S. typhi*), a potent agent for gallbladder cancer, *Streptococcus bovis* (*S. bovis*), a risk factor for colon cancer development, and *Chlamydia trachomatis* is known to cause cervical cancer (Mager 2006). Certain parasites like *Opisthorchis viverrini* (*O. viverrini*) and *Clonorchis sinensis* (*C. sinensis*) which reside inside the human body are also known to increase the risk of cancer. *C. sinensis* is a prime parasite with a 1.86% prevalence rate in Korean population, mainly linked to liver and biliary disorders, especially cholangiocarcinoma (CCA) (Kim et al. 2016). The exact mechanism contributing to cancer caused by *C. sinensis* is not clear but is analogous to carcinogenesis induced by *O. viverrine*. These parasites mainly cause inflammation, release parasite-derived products as well as ROS, which causes physical damage, adduct formation, and anticipate in carcinogenesis (van Tong et al. 2017). Another class of agents that can induce cancer is genotoxins released by certain strains of *Escherichia coli* (*E. coli*) known as colibactin. This colibactin induces tumor growth by regulating the SUMOylation process in the mice model, while colibactin damaged colorectal cells in humans by causing alkylation of DNA, leading to DSBs. These DSBs are hotspots of mutations involved in human carcinogenesis (Dalmaso et al. 2015).

Furthermore, food that we consume is also known to be carrying potential mutagens and accounts for over 99% of the carcinogenic and toxic chemicals to which humans are exposed. Likewise, the feeding onto the processed meat (Group 1 carcinogen) and red meat (Group 2A carcinogen) are also categorized as human carcinogens according to the International Agency for Research on Cancer. The epidemiological data has confirmed the same, but the underlying mechanism for mechanisms of genotoxicity and how cancer is induced is still unclear, particularly the extent to which DNA damage is caused. The literature studies suggest that meat consumption can cause DNA breaks, adduct formation (Pelland-St-Pierre et al. 2021).

Moreover, these mutagens are further classified as naturally occurring compounds, some formed during heating, and others include additives and contaminants (pesticides). The class of mutagenic plant-derived compounds includes pyrrolizidine present in some herbal teas and medicines. These indirect-acting mutagens and their interaction with other

molecules induce DNA strand chromosomal breakage and mutations (Schoental 1968). PAHs are widespread chemical carcinogenic pollutants that are exposed to humans by consuming contaminated food. The dietary PAHs are known to induce colorectal cancer (CRC), but the underlying mechanism remains unclear (Poirier et al. 2019). Even the toxins produced by fungi growing on foodstuffs are also an essential source of mutagenic contaminants referred to as mycotoxins. Some examples of mycotoxins are fusarin, ochratoxin, deoxynivalenol, ochratoxin, etc. They are generally found growing on crops, meat products, milk and eggs, nuts and peanuts, fruits, and many other food items. These mycotoxins produced inhibit DNA and RNA synthesis and induce apoptosis (Ferrante et al. 2012). Also, some mycotoxins can intercalate between the bases of the DNA double helix, which hinders the replication process. As the replication of DNA is affected, it produces teratogenic and mutagenic effects. Furthermore, mycotoxins induce mutations in genes responsible for controlling the cell cycle, leading to cancer development (Claeys et al. 2020). In support of this, nearly ten investigations have found an association between aflatoxin (type of mycotoxin) and liver cancer (Rahman et al. 2020), while two studies reveal an association between ZEN (Zearalenone) and breast cancer (Pillay et al. 2002; Belhassen et al. 2015). Interestingly, the AFB1 itself cannot directly interact with DNA, only the bio-transformed version (AFB1-8, 9-epoxide via cytochrome p450 enzymes) is capable of generating highly mutagenic DNA adducts by irreversibly attaching to guanine residues. Thereby, most countries have put strict regulations about the levels of aflatoxin in food items as high amounts result in DNA adducts formation (Engin and Engin 2019).

Hypoxia-induced DNA damage

The hypoxia (a hallmark of cancer) is a sub-region in the tumor microenvironment (TME) along with nutrient deprivation, low extracellular pH, and high interstitial fluid pressure. The hypoxic condition arises when oxygen consumption by cells exceeds that of supply (Vaupel and Harrison 2004). The hypoxic region is characterized as heterogeneous in nature, with regions of chronic and acute hypoxia, altered pH, and immune infiltration (Hughes et al. 2019). In a hypoxic TME (e.g., 0.2 to 1% O₂), tumor cells slowly adapt to hypoxic conditions where they continue to grow and proliferate with altered/amended cellular biology. In contrast, another microenvironment is known as permanent anoxic (e.g., close to 0% O₂). Tumor or normal cells are leading to cell death (Luoto et al. 2013). A multitude of researches has concluded intrinsic hypoxia biomarkers as HIF-1 α , vascular endothelial growth factor (VEGF), carbonic anhydrase IX (CAIX), osteopontin and glucose transporters 1 and 3 (GLUT1, GLUT3), and the extrinsic biomarkers: drugs that specifically accumulate or

become bio-reduced to form adducts within hypoxic cells such as pimonidazole (PIMO), EF5 and CCI-103 F (Ljungkvist et al. 2007; Le and Courter 2008). Hypoxia cells have defective DNA repair, increased mutation rate, and hypoxia has the capacity to accelerate genomic instability through increased chromosomal rearrangement and decreased centromere function, increased unrepaired DSBs and replication errors, increased gene amplification, and inactivation of intrachromosomal fragile sites (Coquelle et al. 1998; Bristow 2008; Luoto et al. 2013). The study by Kumareswaran et al. found that under hypoxia state, aberrant or compromised DNA-DSB repair of G1-associated DNA-DSBs as a potential factor responsible for increased genetic and/or chromosomal instability (Kumareswaran et al. 2012).

Hypoxia instigates HIF and inducible nitric oxide synthase (iNOS), which results in upregulation of intracellular ROS and RNS, leading to DNA damage in progression with poor prognosis (Kawanishi et al. 2017; Rahman et al. 2020). A consequence of hypoxia in causing genomic instability has been shown beautifully in Figure 2. Still now, how hypoxia links with increases ROS production is still a matter of debate.

One theory supports this hypoxia act on complexes I, II, and III of the electron transport chain (ETC) in mitochondria which drive increased ROS production (Hamanaka and Chandel 2009). ROS plays a pivotal role in stabilizing and activating HIF1 α , which activates survival, proliferation, metastasis, and a tumor cell's metabolic changes. ROS induces intracellular signaling mechanisms involving mitogen activated protein kinase (MAPK) that depends on nuclear factor kappa B (NF- κ B). It can directly activate MMPs synthesis and tissue inhibitor of metalloproteinases (TIMPs), leading to proliferation and invasion of tumor cells (Li et al. 2011). This concludes that ROS continuously or perpetually assist directly or indirectly, to each step of carcinogenesis, from the initiation to the tumor transformation and progression (Singh et al. 2021.; Tafani et al. 2016). Moreover, when hypoxic cells acquire reoxygenated state, this results in further DNA damage due to a sudden burst of free radicals (Hammond et al. 2003). HIF1 α is crucial for tumor adaption to hypoxic, and it is also a key prognostic tumor factor (Fukushima et al. 2017; Han et al. 2019). Its overexpression has been linked with a poor disease outcome and increased patient mortality in

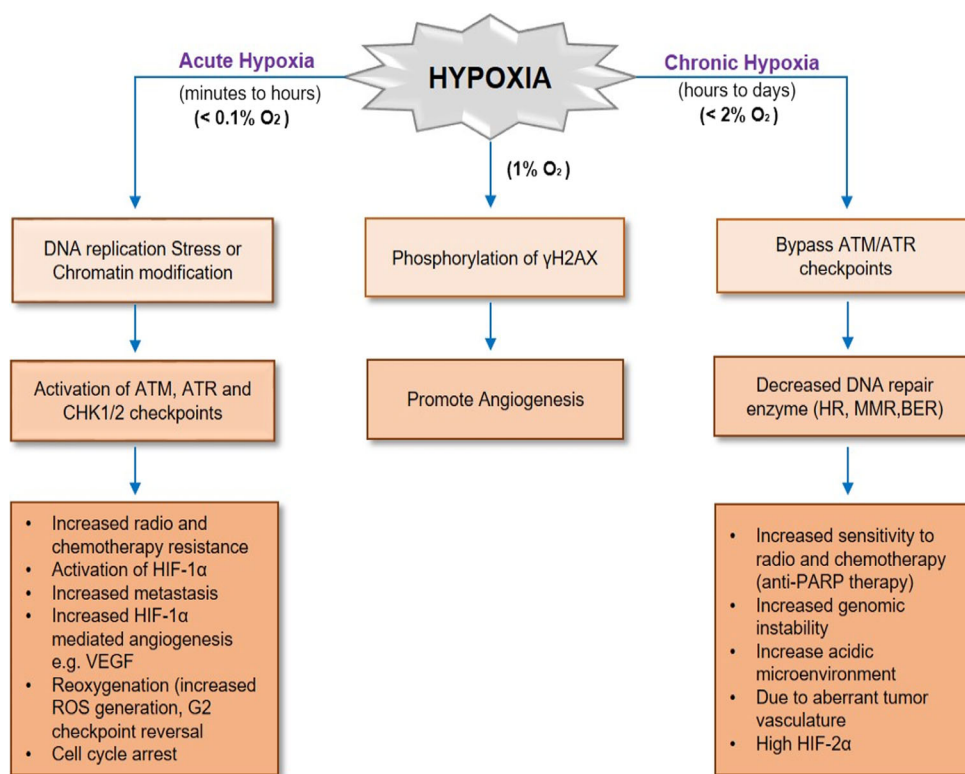


Fig. 2 Schematic of the hypoxia-mediated genetic instability: Cancer cell exposed to acute hypoxia causes DNA damage or compromised DNA replication also known as replication stress which activates ATM–ATR-mediated cell cycle checkpoints to arrest the cell to repair any DNA damage caused by ROS. Due to impaired DNA repair enzyme or non-repaired DNA breaks causes genomic instability, which results in tumorigenesis. Further acute hypoxia causes activation and stabilization of HIF-1 α , promote angiogenesis and which results in radio and

chemotherapy resistance. Whereas chronic hypoxia also gains genetic instability through decreased DNA repair enzymes, leading to increased mutation. It also upregulates the expression of HIF-2 α . ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia- and Rad3-related kinase; ROS, reactive oxygen species; BER, base-excision repair; CHK2, checkpoint kinase 2; HR, homologous recombination; MMR, mismatch repair; PARP, poly (ADP-ribose) polymerase

various cancer such as bladder, brain, breast, cervix, colon, endometrium, lung, oropharynx, pancreas, skin, and stomach cancers (Semenza 2010; Wilson and Hay 2011; Jun et al. 2017; Barrak et al. 2020). Loss of HIF-1 α control can enhance tumorigenesis and genomic instability via cooperation with oncogene c-MYC (c-Myc expression is downregulated in low-oxygen regions of solid tumors) (Okuyama et al. 2010; Li et al. 2020). Moreover, the study by Wang et al. showed that HIF-2 α , another transcriptional regulator of hypoxia, plays a crucial role in regulating the c-Myc expression in chronic hypoxia, and consequently influences 5-FU sensitivity in colorectal cancer by regulating or altering altered the G1/S checkpoint (reason for chemoresistance) (Wang et al. 2016). Furthermore, DNA damage can also be induced by telomeric shortening, or replication stress instigated by oncogene activation and loss of function of tumor suppressor genes (Bartek et al. 2007).

A plethora of studies showed that chronic hypoxia leads to downregulation of DNA damage response (DDR) effectors proteins, such as RAD51 and BRCA1, in cancer. (Bindra et al. 2004, 2005; Meng et al. 2005). Hypoxia also induces replication arrest, which activates DNA damage response through ATR- and ATM-mediated signaling thus leads to induction of p53-dependent apoptosis (Olcina et al. 2010). Alteration in hypoxia affects DNA damage response pathways, including HR, NHEJ, miss-match repair(MMR), nucleotide excision repair (NER), base excision repair (BER), and the Fanconi anemia pathways (Begg and Tavassoli 2020; Kaplan and Glazer 2020). For instance, the downregulation of the NHEJ pathway could sensitize cells to DNA damage following ionizing radiation (IR). In contrast, the HR pathway's downregulation could sensitize cells to DNA crosslinking agents (Chan et al. 2009). Studies suggest that iNOS-dependent 8-nitroguanine formation by HIF-1 α and NF- κ B plays an essential role in tumor progression, and 8-nitroguanine can be a potential biomarker for inflammation-related cancer (malignant fibrous histiocytoma) (Hoki et al. 2007). Furthermore, results show that HIF-1 α and iNOS have the probability of activating or influencing each other to handle fixed DNA damage, resulting in accumulation of mutation, acquiring tumor invasiveness, and poor prognosis (Kawanishi et al. 2017).

A study by Young and et al. found that hypoxia induces aberrant DNA synthesis, leading to DNA over replication and promoting metastasis (Young et al. 1988). Another study by Englander and his co-workers suggests that cerebral hypoxia causes mitochondrial and nuclear DNA damage in the rat hippocampus and cortex (i.e., rat brain) (Englander et al. 1999). Moreover, HIF-1 and HIF-2 in severe tumor hypoxia condition involved in the replication-associated generation of gamma- histone variant 2AX (γ H2AX) in endothelial cells, which leads to neovascularization, and accumulation of γ H2AX enhances a tumor cell's scope to repair DNA

damage, contributing to chemoresistance (Economopoulou et al. 2009; Wrann et al. 2013). Recently, a study by Riffle et al. mentioned the involvement of ATM kinase, but not ATR responsible for γ -H2AX formation (also known as DNA damage marker) in the hypoxic tumor spheroids, which mimic tumor microenvironments of A673 spheroids by hypoxia-induced phosphorylation of H2AX (Riffle et al. 2017). Indeed, hypoxic cells or cells growing in the hypoxic micro-environment acquire gene amplification, point mutations, and increased numbers of DNA strand breaks periodic hypoxia and reoxygenation cycle. These genetic changes cause further activation of oncogenes or inactivate tumor suppressor genes, resulting in a mutator phenotype (Chan et al. 2009)

Mutagenic sensitivity: a biological marker of cancer susceptibility

Comprehensive studies of tumor biology with different methods, including chemical carcinogenesis, molecular biology, developmental biology, biochemistry, and tumor virology, have highlighted the contributing role of genetic and epigenetic mechanisms in tumor development and progression. Carcinogens are the agents which promote cancer growth by altering and interfering with major cellular activities. Recent technological advancements, such as gene expression profiling, next-generation sequencing, and multi-omics analysis, are significant breakthroughs in the molecular characterization of tumors and associated mechanisms as modulated by the carcinogens (Perera and Weinstein 2000). Genetic and epigenetic alterations in the cellular pathways related to growth, differentiation, and death represent the fundamental cause of cancer. Interestingly, genetic and epigenetic mechanisms work sequentially to trigger tumorigenic processes, and these processes can be targeted therapeutically to suppress the cancerous affected region completely. The following sections will shed light on various genetic and epigenetic alterations induced by carcinogens.

Genetic effect of environmental mutagens and carcinogens

Cancer is characterized by continuous genetic alterations, including mutations, DNA damage, copy number variations, gene amplification, chromosomal abnormalities, and gene fusions (Adeola et al. 2021). These genetic aberrations can be specified to a particular segment of DNA or span the whole length of it and ultimately lead to either oncogene activation or tumor suppressor gene inactivation (Chakravarthi et al. 2016). Genetic and chromosomal stabilities are the characteristic features of most cancers, and progress has been achieved in investigating therapeutic options to cure cancer. Moreover, studies have revealed that genetic alterations in non-coding RNA

also promote tumorigenesis by altering promoters' activities, enhancers, and other regulatory elements. MicroRNA (miRNA), the single-stranded RNA molecules, are extensively researched and known to be dysregulated in a variety of cancers (Melo and Esteller 2011). Both genotoxic and non-genotoxic carcinogens are responsible for gene expression changes and support tumor growth and proliferation.

Carcinogenic agents that do not require any modification or activation to cause genetic effects are termed activation-independent carcinogens. These agents, for instance, radiations, nitrosamines, and alkylating agents, can directly interact with DNA and induce disarrangement of genetic material and the formation of DNA adducts. On the contrary, activation-dependent agents, such as, polycyclic aromatic hydrocarbons (PAHs), mycotoxins, and aromatic amines, require phase I or II type metabolic reactions to exert their genotoxic effects (Barnes et al. 2018). Several reactive oxygen species, like hydroxyl radicals and reactive nitrogen species like peroxyxynitrite, are known for their genotoxic effects. ROS-induced damage is the major contributing factor to base modifications, generation of apurinic/apyrimidinic sites, and production of single-strand DNA breaks. Interestingly, ROS-induced damage produces various modified bases, which gets accumulated and promote genetic defects and instability (Kryston et al. 2011). Oxidative damage generated by reactive free radicals further induce DNA-crosslink (DPCs) formation. A couple of studies have confirmed that environmental exposure to ROS/RNS developing substances, such as NiCl₂, sulfur dioxide, arsenite, and benzopyrene, triggers DPCs formation, which further causes interruptions in DNA replication and transcription processes (Kojima and Machida 2020).

Heavy metals like Cr, As, nickel, mercury, and aluminum are considered the ambassadors of mutagenic changes. For instance, pentavalent Cr makes a complex with a guanine base and induces conversion of the base to 8-Oxoguanine that will further cause G to T transversions (Jadoon and Malik 2017). In a study in human recombinant hepatoma cells, chromate (VI) was found to induce transcriptional activation of 13 different promoters that ultimately caused activation of various signal transduction pathways (Tully et al. 2000). Besides this, the carcinogenic effect of nickel was established by many studies as the metal induces DNA damage through DNA binding and production of ROS. The metal also interferes with DNA repair mechanisms, including nucleotide repair, BER, mismatch repair, and homologous and non-homologous recombinational repair pathways (Guo et al. 2019). Surprisingly, nickel was found to regulate the gene expression of various genes such as telomere marker gene, hypoxia-regulated gene Cap43, and several other genes related to mitogenesis (Beyersmann 2002). Additionally, As has also been investigated for its carcinogenic and cytotoxic effects. As is known to promote mutations in tumor protein p53 (T53), interference with DNA repair activities, inhibition of poly ADP-ribosylation, suppression of the transcriptional activity of zinc finger proteins, such as XPA

and PARP1, and ubiquitin-mediated proteolysis of DNA repair enzymes (Muenyi et al. 2015).

Epigenetic effect of environmental mutagens and carcinogens

Epigenetic alterations have a prominent role in triggering cancer-specific characteristics and acquisition of tumor development. Genomic hypo-methylation, hyper or hypomethylation of DNA, and histone proteins' modifications are the major epigenetic features associated with neoplastic cells (Jones and Baylin 2007). Studies have revealed that tumorigenesis is the result of the cumulative effect of various epigenetic modifications. For instance, acetylation of histone proteins H3, H4, methylation of H3K9, and cytosine methylation are observed during gene silencing (Richards and Elgin 2002). DNA methylation, histone methylation, and histone acetylation are reported as the major epigenetic regulatory mechanisms associated with cancer. DNA methylation is a unifying feature of cancers and contributes to the inactivation of transcriptional events and chromatin architecture (Klutstein et al. 2016). Similarly, histone modifications, including mainly acetylation and methylation and phosphorylation, glycosylation carbonylation, SUMOylating, and ribosylation, both at the promoter and targeted level, have a contributory role in tumor development (Kurdistani 2007).

Cumulating shreds of evidence have suggested that both genotoxic and non-genotoxic carcinogens contribute to epigenetic abnormalities associated with cancer (Pogribny and Rusyn 2013). The carcinogenic potential of heavy metals such as aluminum, Cr, nickel in inducing epigenetic changes like the silencing of DNA and tumor suppressor genes have been reported in many studies. Both short and long exposures to arenite cause modifications in DNA methylation patterns. Research with mice exposed to arenite has shown that the increased metal concentration was associated with altered DNA methylation, silencing of cytochrome P450 family members, and upregulation of glutathione S-transferase family members (Xie et al. 2007). Likewise, in lung cancer cells, nickel transformation was linked with the silencing of DNA repair gene O⁶-methylguanine DNA transferase (MGMT) correlated with hypermethylation of MGMT promoter along with chromatin condensation (Ji et al. 2008). Furthermore, the epigenetic potential of trivalent chromium is validated by a study where the metal has induced hypermethylation of CYP1a1 promoter and also silencing of CYP1a1 gene expression by recruiting histone deacetylase 1 (HDAC1) and DNA methyltransferase (DNMT) enzyme (Wei et al. 2004).

Besides heavy metals, gaseous olefin 1,3-butadiene, a monomer used in rubber production, is also known for its carcinogenicity and induced epigenetic alterations. The gas induces genomic instability, chromatin de-compaction, and activation of transposons. Interestingly, it was found that the

loss of methylation at H3K9 and H4K20 was the primary factor responsible for chromatin de-compaction and transcriptional repression (Koturbash et al. 2011). In addition to this, several pharmaceutical compounds, for instance, diethylstilbestrol, a synthetic nonsteroidal estrogen, is a known human carcinogen that causes demethylation and transcriptional silencing of several critical genes related to tumorigenesis such as lactoferrin (Lf), c-fos, and nucleosomal binding protein 1 (Nsbp1) (Pogribny and Rusyn 2013). In parallel, phenobarbital, a non-genotoxic carcinogen, also induces epigenetic abnormalities. It has been reported that the compound induces DNA methylation in genes related to the cytochrome P450 family in experimental tumor mice model (Lempiäinen et al. 2011).

Moreover, many biological carcinogens, such as aflatoxins isolated from *Aspergillus flavus* (*A. flavus*) and *Aspergillus parasiticus* (*A. parasiticus*), are also potent epigenetic regulators. In a study, Zhang et al. demonstrated that exposure to aflatoxin B1 (AFB1) is responsible for hypermethylation mediated inactivation of several tumor suppressor genes RASSF1, MGMT, and p16. They validated their hypothesis by showing a positive correlation between AFB1-DNA levels and methylation patterns of associated genes (Zhang et al. 2002). Similarly, several epigenetic modulations caused by *H. pylori* have been disclosed in gastric cancer studies. *H. pylori* infection is the source of aberrant DNA methylation of several cancer-related genes, including lipoxygenase (LOX), thrombomodulin (THBD), actin-related protein 2/3 complex, subunit p41 (p41ARC), and tumor suppressor p16^{INK4A} (Nakajima et al. 2009).

Relationship between DNA adduct and tumor occupation

DNA adduct is a small piece of DNA that binds to a chemical covalently and causes DNA damage and abnormal DNA replication. The process of adduct formation is considered the initiation of mutational events, and thus DNA adducts serve as potential biomarkers for cancer diagnosis (Rajalakshmi et al. 2015). Early studies in cell culture models have explained that many chemical carcinogens generate DNA adducts and induce mutagenesis. Further, Maher and McCormick's study validated the hypothesis of DNA adducts as they found a strong correlation between the concentration of carcinogens, DNA adduct formation, mutagenesis, and tumor formation (Maher and Justin McCormick 1984). Several studies are available in the literature to define the role of DNA adducts in tumorigenesis. One of the notable examples is aristolochic acid. This chemical induces DNA damage by 7-(deoxyadenosine-N6-yl)-aristolactam I (dA-AL-I) adduct formation as measured in the urothelial tissues of the exposed individuals (Chen et al. 2012). Similarly, UV irradiation-

induced DNA damage in human cancers is another example highlighting the role of DNA adducts. UV-induced damage results in the production of cyclobutane pyrimidine dimers and 6-4 photoproducts that induce CC to TT mutations (Cadet and Douki 2018). Besides, methylating agents, Cisplatin, cigarette smoke, aflatoxin, malondialdehyde, and 4-hydroxynonenal are the well-known DNA adducts (Garner 1998).

The human diet contains several mutagenic and carcinogenic ingredients; therefore, several research groups are interested in investigating the process of DNA adduct formation in diet-related carcinogenic pathways (Hemeryck and Vanhaecke 2016). Mycotoxins, including aflatoxins, fumonisin, sterigmatocystin, and others, have been studied for their carcinogenic potential; however, only AFB1 has been categorized as a human carcinogen. Exposure to AFB1 causes the formation of DNA adducts like AFB1-N7-G through lipid peroxidation, as revealed from studies in hepatocellular carcinoma (Wogan et al. 2004) (Wang and Groopman 1999). AFB1 first transformed itself into carcinogenic AFB1-8,9-epoxide and AFB1-Fapy-Dg, which further reacts with guanine residues to produce mutagenic DNA adducts, which in turn induce cell cycle checkpoint deterioration (Engin and Engin 2019).

Moreover, ptaquiloside found in bracken fern has been associated with the occurrence of bladder and gastrointestinal tumors. Exposure to this carcinogen leads to the formation of DNA adducts ptaquilosin and ptaquilosin dienone with alkylating properties (Hodge 1973). Like so, flavoring substances estragole and methyleugenol are also linked with DNA adduct formation and carcinogenesis. 18 N2-(transisoestragol-3'-yl)-G, N2-(estragole-1'-yl)-G, 7-(transisoestragol-3'-yl)-G, and 8-(trans-isoestragol-3'-yl)-G are the DNA adducts generated from estragole (Paini et al. 2012) while [N6-(transmethylisoeugenol-3'-yl)-A and N2-(trans-methylisoeugenol-3'-yl)-G are DNA adducts resulted from methyleugenol (Smith et al. 2002b).

DNA adducts can be analyzed and measured with different methods, and in the past three decades, various ever-improving ways have been documented. The classical approach is the use of radioactive carcinogens. The method uses either carbon-14 or tritium-based labels and can measure 1 DNA adduct per 10⁶ or 10⁷ nucleotides. The most sensitive physio-chemical method of adduct detection is ³²P-post labeling method/immunoaffinity method. The procedure does not require prior knowledge of the adduct structure and helps detect a wide range of high molecular weight chemical carcinogens such as polycyclic aromatic hydrocarbons, cigarette smoking, and dietary mutagens (Watson 1987). Gas or liquid chromatography-mass spectrometry, based on ionization techniques, is another specific method of adduct measurement. The technique requires hydrolysis or derivatization of carcinogen before quantifying the adduct levels (Gavina et al. 2014).

For instance, a recent study has highlighted the relevance of the high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) technique to quantify 1,N²-propanodGuo adducts generated by reaction between aldehyde and DNA bases (Sanchez et al. 2021b). Fluorescence-based methods have also been exploited as adduct measurement techniques to provide better specificity and sensitivity. A more sensitive version of the technique utilizes fluorescent dyes such as BODIPYFL, and the adducts are separated and then detected by laser-induced fluorescence (Jang et al. 2006).

Additionally, immunoassays with antibodies have been used widely as a method of DNA adduct quantification. Competitive quantitative assays and dot blot assays are the most commonly used immunoassays. A fascinating feature of immunoassays is their sensitivity as they can detect 1 adduct/10⁸ nucleotide; sometimes, the detection will be as specific as 2–3 adducts/10⁹ nucleotides. Another essential feature of these assays is their specificity as the antisera are designed to a particular adduct and can recognize structurally similar adducts related to the same or even different carcinogens classes. The technique has been used widely to measure adducts present in human tissues and blood samples (Brown 2012) (Santella 2018). Recent work described how technological advancements had improved the evaluation of DNA adducts. The advancement of next-generation sequencing (NSG) methods has significantly opened up new avenues for DNA adductome analyses. In this approach, the first step is LC-MS-based analysis followed by validation of biological activities and analysis of mutational signatures. The last step is to measure DNA adduct levels in blood or tissue samples (Totsuka et al. 2021).

Crosstalk between DNA damage and inflammation in multiple steps of carcinogenesis

Inflammation, including both acute and chronic, is induced by multiple factors, including environmental carcinogens (already explained above in review), infectious agents, TME components, and hypoxia. Abundance studies support that inflammation produces free radicals resulting in DNA damage, and free radicals damage healthy cells and causes inflammation (Pham-Huy et al. 2008). Inflammation also results in oxidative stress, which upregulates cancer developments in organs. 8-hydroxy-2-deoxyguanosine has the potential to be used as a biological marker for oxidative stress. Under the exposure of UV radiation or free radical damage, oxidative nucleotide such as glycol, dTG, and 8-hydroxy-2-deoxyguanosine is found to be increased during oxidative damage to DNA (Hattori et al. 1996). In cancer, failed DNA repair mechanism causes unrepaired DNA lesion, which causes a mutation in the genome and further leads to

microsatellite instability and genome instability (Negrini et al. 2010). Studies showed cancer cells, after undergoing apoptosis, release immunogenic cell death (ICD), which activates the host's immune systems (Pham-Huy et al. 2008). How inflammation mediates DNA damage and their crosstalk mechanism and the inflammatory microenvironment's involvement have been explained in upcoming subsections.

Inflammation-mediated DNA damage

Acute inflammation has been linked with a defense mechanism. In contrast, chronic inflammation has been associated with carcinogenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, metastasis, autoimmune, neurological disease, diabetes, etc. (Coussens and Werb 2002; Mantovani 2005). In 1987, the study by Lewis and et al. reported that inflammation and the release of genotoxic oxidants might be one mechanism for carcinogenesis (Lewis and Adams 1987). Under chronic condition not only epithelial cells but also inflammatory cells such as lymphocytes, macrophages, and plasma cells produces reactive oxygen/nitrogen species (ROS/RNS) or reactive oxygen and nitrogen species (RONS), which in turn causes (a) DNA damage including nucleobase oxidation, deamination, halogenation, and alkylation, as well as strand breaks of the phosphodiester backbone, (b) carbonylation (an irreversible and irreparable protein modification induced by oxidative stress) in organs, leading to cancer. A plethora of studies showed that numerous RONS is a potent oxidizing agent. RONS oxidized guanine (known to be the most easily oxidized DNA base) to produce mutagenic 8-oxo-guanine (8oxoG) and 8-nitro-guanine (which is unstable and quickly becomes an abasic site) (Steenken and Jovanovic 1997; Lonkar and Dedon 2011). Thus 8oxoG can lead to G→T transversions mutation, and this is more susceptible to oxidation than its parent guanine, leading to the production of various more stable and mutagenic secondary products such as spiroiminodihydroantoin (Sp), guanidinohydroantoin (Gh), oxazolone (Oz), oxaluric acid (Oa), and cyanuric acid (Ca) (Cheng et al. 1992; Uppu et al. 1996). Murata's review talked about the presence of mutagenic DNA lesions, such as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-nitro-guanine in inflammation-related Cancer (Murata 2018; Singh et al. 2019). In addition to oxidation, RONS can deaminate DNA bases, and deaminated products are mutagenic in nature. Spontaneous deamination of the methylated form of cytosine (5meC) leads to a change base into uracil or thymine (causing C→T transitions). This molecular signature has been found in many cancers. The amount of mutation correlates with the cancer diagnosis stage; thus, this supports cancer-associated inflammation causes deamination and accumulation of mutations (Marusawa et al. 2011). Further, inflammatory cells also secrete hypohalous acids, which react with

DNA during inflammation to form the adducts. For example, neutrophils secrete the myeloperoxidase enzyme to produce hypochlorous acid (HOCl), and eosinophils secrete eosinophil peroxidase to produce hypobromous acid (HOBr). Inevitably, the halogenated nucleobase, 5-chlorocytosine (5CIC), has a greater possibility to accumulate than oxidative deamination, and thus 5CIC has been assigned a biomarker for chronic inflammation (Kay et al. 2019). DNA damage causes inflammation contributes to genomic instability (a hallmark of cancer) (Negrini et al. 2010), and both inflammation and genome instability share a complex relationship. A positive feedback loop occurs where DNA damage can trigger cell cycle arrest, apoptosis, senescence, and necrosis, of which the latter two can aggravate inflammation (Aoshiba et al. 2013). This feedback loop is deliberately regulated by DNA repair pathways, transcription factors, and cellular signals. Failure of DNA repair mechanism or unrepaired DNA damage from inflammation helps develop cancer by increasing mutagenesis. A study by Jaiswal et al. reported that inflammatory cytokines (such as IL-1 β , IFN- γ , and TNF- α) induce DNA damages and compromise DNA repair activity via a nitric oxide(NO)-dependent mechanism (Jaiswal et al. 2000). NO at a concentration less than 400 nM act as signaling molecules, but innate immune cells produce high levels of superoxide ($O_2^{\cdot -}$) and enzymes that contribute to RONS production along with radicals (e.g., superoxide, hydroxyl radical $\cdot OH$, and nitrogen dioxide NO_2^{\cdot}), anions (e.g., peroxyxynitrite $ONOO^-$, and nitroperoxycarbonate $ONOOCO_2^-$), anhydrides (e.g., nitrous anhydride N_2O_3), hypohalous acids (e.g., hypochlorous acid HOCl and hypobromous acid HOBr), and hydrogen peroxide (H_2O_2). Moreover, pro-inflammatory cytokines energizing intracellular RONS production (Kay et al. 2019). ROS (being secondary messenger), hypoxia, and DNA damage contribute to the signaling cascade of receptors (e.g., members of the Toll-like receptors (TLRs) or nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that instigate pro-inflammatory innate immune response through an array of functionally diverse downstream signaling elements (e.g., NF- κB , STAT1, IRF-3, and caspase-1 activation) (Pálmai-Pallag and Bachrati 2014) also cytokines such as IL6, STAT3, and TNF- α (Kidane et al. 2014). Moreover, damaged DNA leads to upregulation of IRF7 and phosphorylation of IRF3, resulting in its translocation to the nucleus from the cytoplasm, where it functions as the transcription factor. IRFs lead to the production of type IFNs and pro-inflammatory factors (Brzostek-Racine et al. 2011). Besides this, DNA damage influences activation of ATM and a series of consecutive post-translational modifications such as SUMOylation, phosphorylation, and ubiquitination of NEMO in the nucleus, which are vital for signal transduction to activate NF- κB (McCool and Miyamoto 2012). Other studies show NF- κB activates the human IFN- $\lambda 1$ gene, IRF-1, and IRF-7 that can further impact the expression of IFN- α and

IFN- λ genes (Brzostek-Racine et al. 2011). NF- κB , transcription factor regulates expression of several pro-inflammatory gene products such as TNF and its family, IL-1a, IL-1b, IL-6, IL-8, IL-18, chemokines, MMP-9, VEGF, COX-2, and 5-LOX, leading to tumorigenesis by inhibition of apoptosis, proliferation, angiogenesis, invasion, and metastasis. Numerous studies support tumor-producing inflammation can stimulate NF- κB , resulting in iNOS -dependent DNA damage. Moreover, studies also showed that hypoxia induces hypoxia-iNOS, which increases intracellular RNS and ROS free radicals concentration, resulting in DNA damage with poor prognosis (Janssens and Tschopp 2006; Kawanishi et al. 2017). The growing evidence of studies in the inflammation area suggests that carcinogens (such as cigarette smoke), tumor promoters, carcinogenic viral proteins, chemotherapeutic agents, and γ -irradiation induces NF- κB (Aggarwal et al. 2006). Anti-inflammatory drugs have the ability to target NF- κB and its regulated genes, and thus have the potential for targeting cancer (Yu et al. 2020). A study by Sokolova and Naumann mentioned human pathogen *H. pylori*, immune cells, and epithelial cells create inflammatory environments by promoting oxidative stress (stimulate the production of RONS) that results in DNA damage, apoptosis and cell proliferation in gastric mucosa, which leads to intestinal metaplasia and gastric carcinogenesis. Further, bacteria *H. pylori* can stimulate RONS production in immune cells. RONS is toxic to mitochondrial DNA (mtDNA), causing genome instability and loss of homeostasis (Calvino-Fernández et al. 2008; Sokolova and Naumann 2019). Released extracellular or intracellular oxidized mtDNA (mtDNAox) fragments released from cells act as mediators of immune response via DAMP that further activates TLR9 receptor signaling. Other researchers have also studied the relationship between DNA damage and chronic inflammation in human cancer (Kawanishi et al. 2017). Prolonged inflammation hampers the DNA repair mechanism (downregulates MMR and BER mechanism), which eventually leads to cancer.

Tumor microenvironment-induced inflammation followed by DNA damage

Tumor cells generate an inflammatory microenvironment that encourages tumor cell proliferation and survival, ECM degradation and remodeling, abnormal vasculature, immune cell infiltration. These collaboratively facilitate growth which enables cancer progression (Coussens and Werb 2002). The solid tumor shows inflammation in the inflammatory microenvironment; immune cells like neutrophils, macrophages release NO, and superoxide ($O_2^{\cdot -}$). During injury or inflammation sites, neutrophils and macrophages migrate and produce extracellular ROS and RNS. Moreover, at the infection site, neutrophils and macrophages generate an array of including

superoxide (O_2^-), H_2O_2 , $HOCl$, NO^* , and NO_2^* radicals (Mittal et al. 2014). ROS and RON are chemical components of inflammation with free radicals, containing one unpaired electron (Biswas et al. 2017). UV-A or γ -irradiation, drugs, heavy metals, etc., are the exogenous source and oxidative metabolism, apoptosis, bystander cells, or enzymatic activity are an endogenous source of oxidative stress mediating ROS production (Pálmai-Pallag and Bachrati 2014). NO is long-lived free radicals that diffuse through the extracellular matrix (ECM). They enter the nucleus by crossing through the plasma membrane and the cytoplasm of epithelial cells; in contrast, O_2^- is barely long-lived to react with DNA inside the epithelial cells' nucleus. Alternatively, inflammatory cells also secrete cytokines (TNF- α) to induce O_2^- accumulation in neighboring epithelial cells (Grivennikov et al. 2010).

Ning and a co-worker mentioned the presence of powerful DNA lesions in cancer and inflammatory cells in the stroma of nasopharyngeal carcinoma (NPC) patients. Further, iNOS expression was spot in the cytoplasm of cancer cells positive for 8-nitroguanine (Ma et al. 2008). Another essential component of TME is hypoxia, which is a characteristic feature of both tumors and inflammation. HIFs are the indispensable regulator of tumor inflammation (Mamlouk and Wielockx 2013; Triner and Shah 2016). The hypoxic condition leads to high-mobility group box-1 protein (HMGB1) translocation of HMGB1 to the cytoplasm from the nucleus (Kang et al. 2013). HMGB1 also release in the extracellular environment by two mechanisms, including active and passive release. Activated immune cells (e.g., macrophage and monocytes) actively release, whereas damaged or necrotic cells participate in the passive release of HMGB1 in the environment. Active HMGB1 release encourages neutrophil recruitment, activation of dendritic cells, and the release of pro-inflammatory cytokines, such as TNF- α and IL-6, from macrophages (Yun et al. 2021). Extracellular secreted HMGB1 from cells encourage various cellular functions, including proliferation, inflammation, and angiogenesis, along with hampering host anti-cancer immunity, which together contributes to tumorigenesis (reviewed in (Wang and Zhang 2020)). Besides, HMGB1 activates the pro-inflammatory signaling pathway and is involved in forming an inflammatory bone-marrow microenvironment (Yuan et al. 2020). The interplay of HMGB1 with RAGE, TLR2, TLR4, and TLR9 (receptor for HMGB1 CpG-DNA complex) transduces cellular signals through a customary pathway that instigate the NF- κ B pathway, and it also interacts with CXCL12/CXCR4 to activate the NF- κ B pathway and thus facilitating the adhesion and survival of malignant cells (Ibrahim et al. 2019). The CXCL12 (SDF-1)/CXCR4 axis is associated with tumor progression, angiogenesis, metastasis, and survival by stimulating various signaling pathways, such as ERK1/2, Ras, p38 MAPK, PLC/MAPK, and SAPK/JNK (Zhou et al. 2017). Numerous studies showed that ROS and RNS induce ICDs in cancer cells, which further

enhance HMGB1 expression and HMGB1-DNA forms a complex leading to NO generation 8-nitroguanine formation (Sokolova and Naumann 2019). Indeed, the HMGB1 and TIM-3 interaction promotes VEGF secretion and thus promotes tumor angiogenesis. This interaction can be a potential target for tumor immunogenic chemotherapy and development (Yasinska et al. 2018). Moreover, data by Parker et al. allude HMGB1 facilitates MDSCs differentiation in the bone marrow and hampers the activation of antigen-driven CD4+ and CD8+ T cells (Parker et al. 2014; Tachibana 2018). More importantly, NF- κ B is an essential player in inflammation, which also regulates iNOS expression. Abundant published evidence suggests that pro-inflammatory cytokines such as TNF- α and IL-6 induce iNOS expression, leading to the formation of mutagenic DNA lesions and carcinogenesis under the inflammatory microenvironment (Sokolova and Naumann 2019).

Another type of inflammation developed in response to anti-cancer therapies (chemotherapy, radiotherapy, immunotherapy, targeted therapy, etc.) is therapy-induced inflammation. Dying cells release DAMPs such as ATP, calreticulin, and HMGB1, which stimulate immune-stimulatory cytokines and enhance the release of tumor neo-antigens which activate de novo anti-tumor T cell responses or may be responsible for immunosuppression. This response is context-dependent and varies with individual and cancer types. Different cells present in TME, such as myeloid cells and fibroblasts and infiltrating cells, produce cytokines and growth factors such as TNF, EGF, IL-6, Wnt ligands. These growth factors may lead to chemoresistance as they are responsible for therapy efficiency used for treatment (Greten and Grivennikov 2019). TNF- α is probably an essential EMT-promoting cytokine and contributes to invasion in many cancers (Sistigu et al. 2017).

A recent study by Srivatsa and co-workers suggested that enhanced expression of EGFR in myeloid cells from colorectal fibroblast is a significant factor in therapy resistance and linked with tumor progression and reduced survival time of colorectal cancer patients (Srivatsa et al. 2017). This is also supported by another study by Halbrook et al., where they have mentioned how the release of pyrimidines such as deoxycytidine from tumor-associated macrophage (TAM) inhibits gemcitabine therapy and is responsible for developing gemcitabine resistance in patients with pancreatic ductal adenocarcinoma (PDA) (Halbrook et al. 2019). Further, the plethora of studies showed that inflammation influences EMT on several levels (because the microenvironment is composed of inflammatory cells and inflammatory mediators, such as cytokines and chemokines, which strongly contribute to the EMT program) (Jing et al. 2011; Suarez-Carmona et al. 2017). Moreover, EMT has also been mediated and activated by (a) stimuli triggered by stromal cells and ECM components of the surrounding microenvironment, (b) soluble factors [epidermal growth factor (EGF), fibroblast growth factor (FGF),

hepatocyte growth factor (HGF), PDGF, TGF- β and VEGF, and (c) morphogens Wnt, Notch and Sonic hedgehog, and pro-inflammatory cytokines (i.e., IL-6, IL-8, TNF- α) (Sistigu et al. 2017), also, inflammatory microenvironment (Sistigu et al. 2017). Various cytokines, such as TNF and IL-1 β , can alter the expression of transcription factors Twist and Slug involved in EMT (Ricciardi et al. 2015; Suarez-Carmona et al. 2017). A study by Labelle and his colleague showed direct interaction of cancer cells with platelets, resulting in EMT and synergistically activating the TGF β /Smad and NF- κ B pathways in cancer cells, promoting invasion metastasis (Labelle et al. 2011).

In solid tumors such as breast, head and neck, pancreatic, lung, brain, prostate, and cervix, DSB repair mechanisms get profoundly influenced by TME cellular and non-cellular factors including hypoxia, inflammation, genotoxic stress, cellular metabolism, and the immune system. The role of the TME and its relationship with DNA damage is emerging as an essential consideration in developing anti-cancer therapy that targets DNA repair-deficient cancer cells. This tumor-TME-DNA damage relationship needs new insights. It is a critical area of investigation to treat cancer (Lama-Sherpa and Shevde 2020) effectively. The interrelationship between inflammation, ROS generation, cellular physiology, and pathology in tumor cells and their microenvironment is described in Figure 3.

Expanding focus on DNA damage in cancer immunotherapy: a sting in a tail

Numerous exogenous and endogenous insults result in DNA damage, and multiple DNA repair mechanisms are available in humans. DNA damage and repair mechanisms have been investigated in various cancers and play an essential role in carcinogenesis. Cancer cells have relaxed DNA repair mechanisms and are characterized by the property of resistance to cell cycle checkpoints that allow continuous proliferation and tumor formation. The concept of DNA damaging chemotherapeutics in various cancers has a long history. For example, the first compounds as DNA damaging agents that entered the market were DNA intercalating alkylating agents such as Carmustine, Lomustine, and Semustine, which modify DNA bases by forming cross-linkages (Nikolova et al. 2000). Similarly, other compounds inducing DNA damage effect are platinum compounds such as Carboplatin, Cisplatin, Oxaliplatin induce DNA damage by forming DNA crosslinks (Hato et al. 2014); antimetabolite DNA antagonists like 5-Fluorouracil, Gemcitabine, Floxuridine, 6-mercaptopurine, Fludarabine, Cladribine induce DNA damage by generating replication interference (Tiwari 2012); and topoisomerase inhibitors such as Etoposide, Doxorubicin, Daunorubicin, interfere with DNA function by inhibiting the DNA-protein complex stability (Buzun et al. 2020) (Cheung-Ong et al. 2013).

Although chemotherapeutic DNA damaging agents have been investigated for their anti-cancer properties in various cancers, several adverse outcomes are also reported. The problems associated with chemotherapeutic agents have moved the focus of cancer therapy towards an immunotherapeutic approach.

Recent investigations have suggested an interplay exists between DNA damage repair and the immune system. This crosstalk has opened up the possibilities of modulating DNA by targeting immune system-related mechanisms, as explained in Figure 4. Studies have reported that DDR defects activate the host immune system by activating the STING pathway, which results in interferon production and amplification in T cell response. Studies in DDR-deficient breast cancers have found activation of cGAS/STING/TBK1/IRF3 pathway with enhanced interferon production, increased production of tumor-infiltrating lymphocytes (TILs), and upregulation in the activity of TANK-binding kinase 1 (TBK1) (Parkes et al. 2017). One of the essential mechanisms regulated by the DNA damage repair system in tumor cells is neo-antigen production. The mutations that arise due to failed DNA damage and genomic instability trigger the production of tumor-specific neo-antigens presented on cell surfaces that will be recognized by T cells and produce an anti-tumor response (Yarchoan et al. 2017). DDR deficiencies in cancers promote the frequency and occurrence of non-synonymous mutations that lead to a new peptide formation. For instance, the high somatic mutational rates and abnormal chromosomal numbers promote neo-epitope formation in BRCA1/2 tumors (Strickland et al. 2016). Another crucial mechanism to be considered is the activation of immune responses by apoptotic signals produced by damaged cancer cells. The apoptotic cells secrete HMGB1 proteins, which in turn stimulate T cell immunity by promoting myeloid differentiation factor 88 (MyD88)/Toll-interleukin 1 receptor domain-containing adaptor inducing INF- β (TRIF) signaling (Apetoh et al. 2007).

Furthermore, the cellular DDR machinery also induces the release of pro-inflammatory cytokines within the tumor microenvironment. A study has shown that DNA damage causes the release of pro-inflammatory cytokines TNF- α and IL-6 (Karakasilioti et al. 2013). Studies in DDR-deficient breast cancer cells have also shown enhanced production of chemokines CXCL10 and CCL5, creating a pro-inflammatory environment in cells (Parkes et al. 2017). Additionally, DNA repair also regulates the expression of programmed death-ligand 1 (PD-L1) through the STAT-IRF1 pathway. For instance, loss of DNA repair proteins was associated with increased PD-L1 expression after radiotherapy and chemotherapy treatment. Similarly, activation of the STING pathway after DNA damage has also been associated with increased PD-L1 expression. STING pathway activation increases the transcriptional activity of type-I IFN and other cytokines after DNA damage (Grabosch et al. 2019). A study has also demonstrated the role of DSBs in

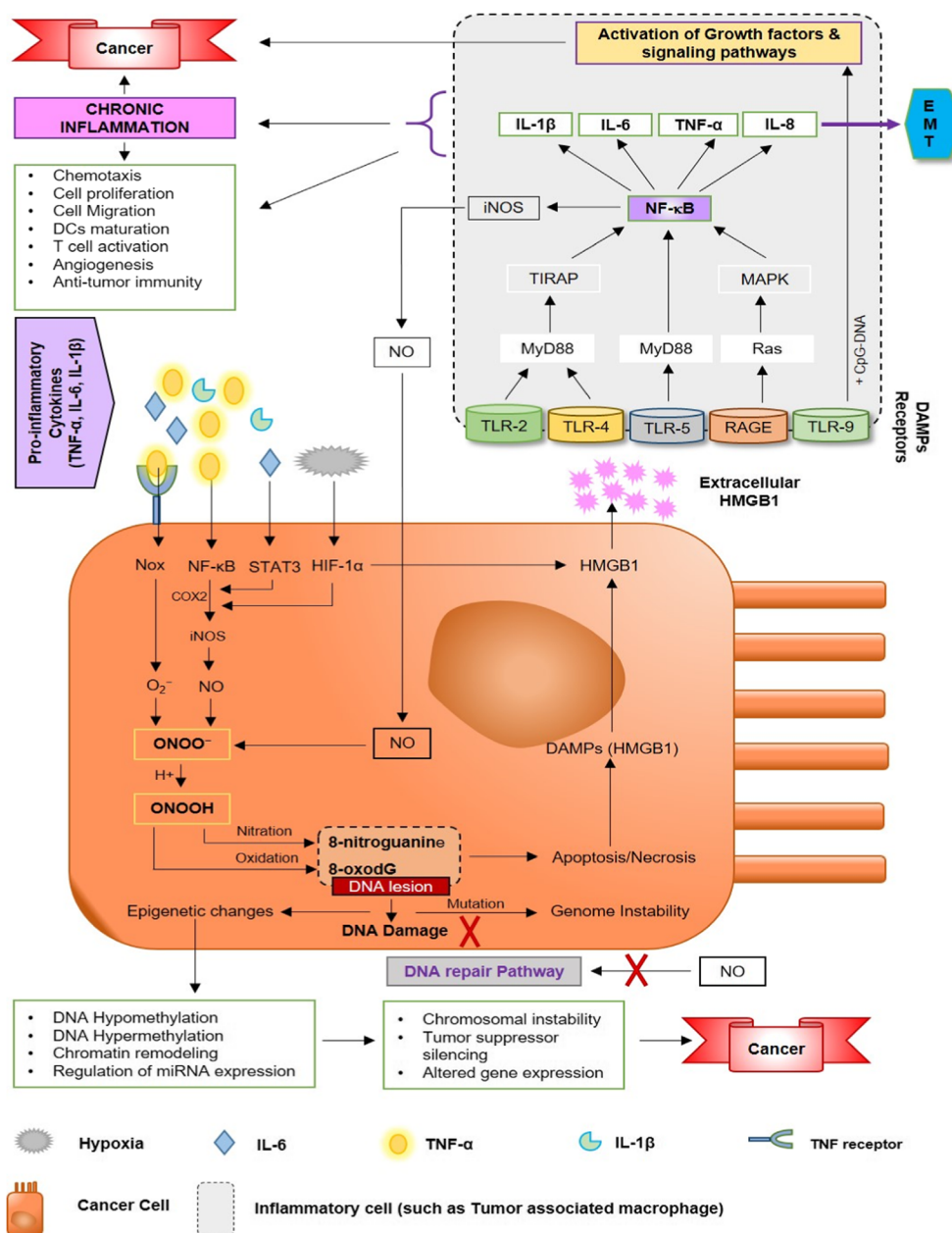


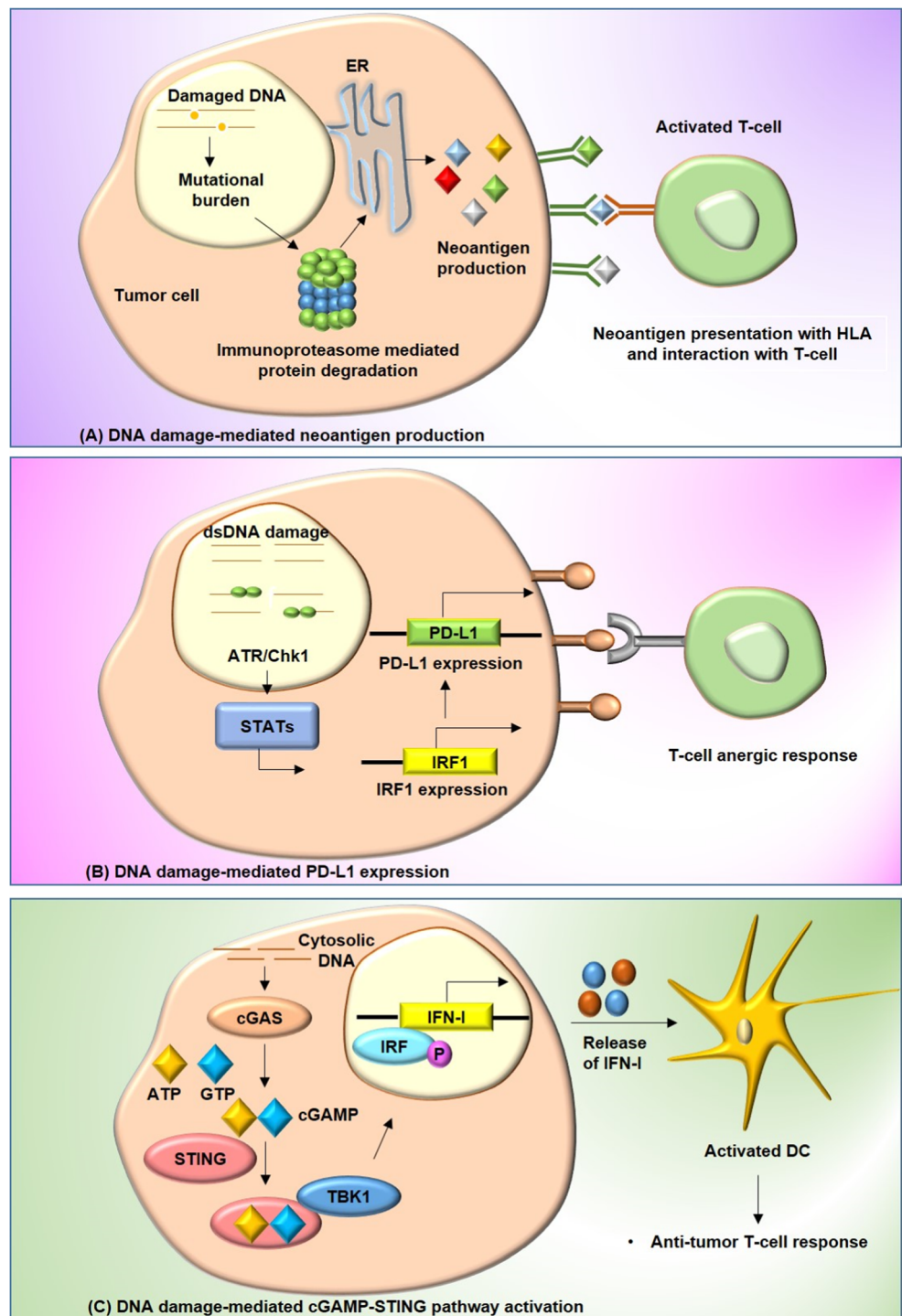
Fig. 3 Schematic presentation of interrelationship between inflammation, ROS generation and cellular physiology and pathology in tumor cells and its microenvironment: Inflammatory cells (such as macrophage) secrete cytokines such as TNF- α in the tumor microenvironment to stimulate O_2^- formation via Nox where it reacts with NO, which is generated by especially iNOS to form $ONOO^-$. This causes DNA lesions (8-nitroguanine, 8-oxodG) in epithelial cells, which damage DNA. NO and ROS suppress the DNA repair mechanism, which results in genetic alteration (i.e., genomic instability) and epigenetic changes. Moreover, the epithelial cell containing damages DNA undergoes apoptosis, where HMGB1 (a nuclear protein), act as DAMPs translocate to extracellular space from nucleus. It is a crucial pro-inflammatory cytokine in its

secretory form. Extracellular HMGB1 binds to different receptors include RAGE and TLRs. The effects of HMGB1 are executed through multiple signaling pathways, including NF- κ B (p65) and MAPK. Various cytokines IL-8, IL-6, IL-1 β , TNF- α release in environment and resulted in tumorigenesis and chronic inflammation. Moreover, macrophage also produces NO (sufficiently long-lived to diffuse through the extracellular matrix) and enter epithelial cells to mediate DNA damage. In addition, IL-8 mediates HMGB1-induced tumor angiogenesis and EMT. Together all lead to cancer. iNOS, inducible nitric oxide synthase; DAMPs, damage-associated molecular patterns; HMGB1, high mobility group 1 protein; EMT, epithelial-mesenchymal transition

regulating PD-L1 expression in cancer cells in an ATM/ATR/Chk1-dependent manner, and activation of Chk1 is the critical step in regulating PD-L1 expression. The

study has also reported that activation of canonical STAT1/STAT3 and IRF1 pathways are associated with DSB mediated PD-L1 upregulation (Sato et al. 2017).

Fig. 4 Role of DNA damage in anti-tumor immune response. **(A)** DNA damage leads to abnormal transcription and translation that leads to the formation of peptides known as neoantigens. The neoantigens, after their synthesis, are transported to the cell surface and are presented in the HLA-neoantigen complex. This complex interacts with T cell surface receptors and promotes T cell activity against tumor cells. **(B)** The double-stranded breaks produced during DNA damage regulate PD-L1 expression in ATR/Chk1/STAT/IRF1-dependent manner. The PD-L1 expresses on tumor cells and interacts with PD-1 on the surface of T cells, and induces T cell anergy. **(C)** In response to DNA damage events, the DNA sensor cGAS binds to the DNA encapsulated in micronuclei and catalyzes the synthesis of cGAMP from ATP and GTP. cGAMP then activates the STING pathway and induces IRF3 expression by regulating TBK1 kinase. This leads to the synthesis of Type-I interferons (IFN-1). This further improves dendritic cell (DC) cross-presentation to enhance T cell activation



The immune mechanisms governed by DNA damage and associated mechanisms have developed a recent interest in developing immunotherapeutic anti-cancer agents. Several combinatorial therapeutic regimens involving DNA-damaging agents and immune-checkpoint inhibitors (ICIs) are being developed. This strategy may help to enhance genomic instability and immune system activation. As per the work published by Brown et al., about 200 clinical trials are

ongoing for various cancers with DNA damaging agents and ICIs (Brown et al. 2018). Some studies have shown that deficiency in DNA repair pathways is associated with immune checkpoint blockade (ICB) response. Similarly, studies have shown that tumors with mismatch repair deficits have shown enhanced neo-antigen production and immune system activation when treated with PD-1 inhibitors (Le et al. 2017). Various poly adenosine diphosphate-ribose polymerase

(PARP) inhibitors have been investigated in experimental and clinical studies to show the PD-L1 inhibitory effect. For example, Olaparib, a PARP inhibitor, has increased PD-L1 blockade in BRCA-deficient tumor cells, and Rucaparib also improved anti-PD-L1 treatment in BRCA mutant tumors (Lamberti et al. 2020). In a recent clinical study named KEYNOTE-365, the efficacy of DDR inhibitor combined with immunotherapy has been explored. The study was based on the intervention of Pembrolizumab, a PD-1 inhibitor, along with Olaparib, a PARP inhibitor. The therapy's primary response reduced serum prostate-specific antigen (PSA) levels (Yu et al. 2019). Besides PARP inhibitors, several other DDR inhibitors, such as ATM, ATR, CHEK, and WEE1, have also been studied in combination with immunotherapeutic agents. A summary of various ongoing clinical trials has been provided in Table 1.

Impact of DNA repair on mutational signatures of environmental mutagens

Base excision repair in mammals and related signaling

DNA lesions arising from various endogenous and exogenous mutagens in the environment cause loss of DNA bases due to hydrolytic cleavage, modification of the bases due to oxidation, methylation of non-enzymatic origin, leading to chemical alteration in the integrity of nucleic acid (Nature 2003). Frequent alteration in the DNA is necessary to be rectified, therefore, achieved using base-excision repair pathway BER. BER is an important asset in governing genomic stability and embroils various diseases such as cancer, aging prompting the establishment of various neurodegenerative disorders ([CSL STYLE ERROR: reference with no printed form.]). Purified enzymes such as DNA-glycosylase specific to DNA recognize the damaged DNA bases and cause cleavage of the glycosylic bond (linking DNA bases to the phosphate backbone) (Lindahl 1979). Another enzyme that adds to the repairment machinery of BER includes a DNA polymerase, AP endonuclease I (APE1), and a ligase (Mitra et al. 1997). AP endonucleases' activity generates a 3-OH and a 5' terminus containing a deoxyribose phosphate (deoxyRP) to 5'-to the abasic site, resulting in a DNA single-strand break (SSB). Further, DNA polymerase β (Pol β), XRCC1, and DNA ligase III α (Lig III) add up by filling the gap generated in between the nucleotide due to the removal of the base that was affected with a lesion (Dianov 2011). In short, patch BER (single nucleotide BER), DNA Pol β embeds the missing base with the subsequent nick fixed by DNA ligase III complexed to XRCC1, therefore accomplishing DNA repair.

In contrast, in long patch BER, a polymerase (β , δ , ϵ) fills within a base gap. It keeps synthesizing DNA, whereas

replacing the DNA downstream of the initial damage site produces a flap (2-13 nucleotides gap) of DNA removed by flap endonuclease-1 (FEN-1) in a PCNA-dependent manner. This long patch BER is sealed by DNA ligase I. The choice of whether or not repair is accomplished via short, or long patch BER chiefly depends on whether or not the abasic sugar is altered or reduced, as Pol β cannot eliminate a changed sugar. If the 5' sugar is modified, it is not removed by Pol β , and a long patch BER is initiated (Dianov 2011; Torgovnick and Schumacher 2015). OGG1 (8-oxoGuanine DNA glycosylase 1) and MYH (MutY DNA glycosylase) are most studies of nuclear glycosylases because of their involvement in recognizing and removing ROS-induced oxidative DNA lesions (8-oxoGuanine) (Fayyad et al. 2021). Loss of OGG1 protein has been linked with lung, ovarian, and skin cancer. Missense mutation and a nonsense mutation in OGG1 have been reported in lung and breast cancer, respectively. Whereas increased expression of APE1 and XRCC1 has linkage with solid tumor and poor survival (Yuan et al. 2017). Methoxyamine, a small molecule that targets AP-site and blocks repair by APE1 enzymes, leads to the accumulation of DNA damage, hence introducing apoptosis.

Similarly, E3330 and Gossypol/AT101, NF- κ B, and BCL2 inhibitors bind to APE1 and use alone or in combination with other chemotherapeutic agents for patients with lymphoma, prostate, lung, and glioblastoma cancers (Grundy and Parsons 2020). Moreover, Jones et al. study showed that biallelic mutations in the BER DNA glycosylase "MYH" result in adenomatous colorectal polyposis with substantial-high colorectal cancer risk (Oishi et al. 2002). Several research showed dysfunctional BER mechanisms linked with cancer (Maynard et al. 2009). On the same note, Lee et al. reported a deficiency in XRCC1 enzyme in breast cancers and studied DNA damaging agent's involvement in causing malfunctioning of BER enzyme, which proposed defects in BER as targets for therapeutic intervention in TNBC (Lee et al. 2019). In summary, the BER repair pathway components have been progressively recognized as promising and potential surrogate biomarkers, therapeutic cancer targets (Kumar 2020).

Environmental mutagens and DNA mismatch repair

Inadvertent incorporation of a nucleotide during the DNA replicative machinery despite the precise functioning by various DNA polymerases (ϵ and δ) leads to a mismatch in DNA bases. DNA proof-reading being the first line of defense when unable to rectify the mis-incorporated base sequences then causes the activation of the mismatch repair (MMR) pathway. Inactivation of genes involved in MMR due to interaction of mutagenic factors then leads to the occurrence of various mutator phenotypes (Zhang et al. 2005). Mismatch repair is also known to be associated with mutagenic insults induced

Table 1 Selected examples of clinical trials of combinatorial DDR and ICI agents for cancer treatment

Clinical trial ID	Phase	Tumor type	DDR agent	ICI agent	Current status	Start year
NCT04276376	II	Solid tumors*	Rucaparib (PARP inhibitor)	Atezolizumab (PD-1 inhibitor)	Recruiting	2020
NCT04266912	I/II	Solid tumors	M6620 (ATR inhibitor)	avelumab (PD-L1 inhibitor)	Recruiting	2020
NCT04187833	II	Melanoma	Talazoparib (WEE-1 inhibitor)	Nivolumab (PD-1 inhibitor)	Recruiting	2019
NCT04158336	I/II	AST	ZNc3/Talazoparib (PARP inhibitor)	Pembrolizumab (PD-1 inhibitor)	Recruiting	2019
NCT03594396	I/II	TNBC	Olaparib (PARP inhibitor)	Durvalumab (PD-1 inhibitor)	Recruiting	2018
NCT03598270 (ANITA)	III	Ovarian cancer	Niraparib (PARP inhibitor)	Atezolizumab (PD-1 inhibitor)	Recruiting	2018
NCT03602859 (FIRST)	III	Ovarian cancer	Niraparib (PARP inhibitor)	Dostarlimab (PD-1 inhibitor)	Active, not recruiting	2018
NCT03522246 (ATHENA)	III	Ovarian cancer	Rucaparib (PARP inhibitor)	Nivolumab (PD-1 inhibitor)	Active, not recruiting	2018
NCT03565991	II	Solid tumors	Talazoparib (PARP inhibitor)	avelumab (PD-L1 inhibitor)	Active, not recruiting	2018
NCT03061188	I	Solid tumors	Veliparib (PARP inhibitor)	Nivolumab (PD-1 inhibitor)	Active, not recruiting	2017
NCT03061188	I	Solid tumors	Veliparib (PARP inhibitor)	Nivolumab (PD-1 inhibitor)	Active, not recruiting	2017
NCT03334617	II	NSCLC	AZD6738	Durvalumab (PD-1 inhibitor)	Recruiting	2017
NCT02861573	I/II	CRPC	Olaparib (PARP inhibitor)	Pembrolizumab (PD-1 inhibitor)	Recruiting	2016
NCT02657889	I/II	TNBC	Niraparib (PARP inhibitor)	Pembrolizumab (PD-1 inhibitor)	Active, not recruiting	2016
NCT02571725	I/II	Germline BRCA mutant OC	Olaparib (PARP inhibitor)	Tremelimumab (CTLA-4 inhibitor)	Active, not recruiting	2015
NCT02264678	I	Head, neck and lung cancer	Ceralasertib (ATR inhibitor)	Durvalumab (PD-1 inhibitor)	Recruiting	2014

during DNA damage. These comprise lesions generated due to oxidative DNA, lesions affecting nucleotides arising from helix distortion, and nucleotides' synthesis due to methylations. Six MMR proteins are generally required in the proper functioning of this repair machinery. Studies have shown that endogenous mutagens, when they interfere with either of these MMR-related proteins (MSH6, PMS1, MLH1, MSH2, PMS2), lead to hereditary nonpolyposis colon cancer (HNPCC) (Vasen et al. 1996; Aarnio et al. 1999). Mismatch occurring in any nucleotide sequence is identified by the formation of a heterodimer comprising of MSH2 protein and MSH3/MSH6 (Kolodner 1999). The occurrence of mismatch in the DNA causes a metabolic shift from ADP to ATP that causes a change in the confirmation of nucleotides, thereby converting MSH2/MSH6 assembly to a sliding clamp, further diffusing with the phosphate backbone of DNA in hydrolysis-independent manner.

Further, heterodimer complex (MLH1 and PMS2) or MLH1 and PMS1 mediates the foreplay between recognition of mismatched bases and proteins crucial for MMR. This assembly then binds with the complex containing DNA polymerases (δ and ϵ), proliferative cell nuclear antigens (PCNA), replication factors (SSD-binding proteins), and a helicase. MMR is known to be the suppressor of mutagenicity and elevates the level of checkpoint activation and induction of apoptosis by various ionizing radiation such as UV. Sites, where damage due to UV radiation occurs, are then occupied by the MMR heterodimers (MSH2-MSH6) that selectively bind to the mismatched bases and not binding with the matched nucleotides adjacent to the photolesions (Hong et al. 2008). Other metabolic components of mismatch repair machinery include SSD-binding protein RPA, HMGB1, and the RCF protein. RPA seems to be involved in every MMR stage as it binds with the nicked heteroduplex DNA much before the mismatched-provoked excision is stimulated by the Mut-S α /Mut-L α . This stimulation protects the ssDNA gapped sequences from excision and thus facilitates the resynthesis of DNA. Studies have shown that phosphorylation reduces the RPA for DNA, unphosphorylated RPA causes stimulation of DNA excision more efficiently as compared to phosphorylated RPA (Dzantiev et al. 2004; Ramilo et al. 2002).

Damage to the DNA by various alkylating agents such as N-methyl-N'-nitrosoguanidine (MNNG), procarbazine, and temozolomide are cytotoxic in nature that can kill cells that are replicating. As these cells progressively acquire resistance hence, they become deficient in MMR. Studies have shown that human colorectal cell lines are resistant to various alkylating agents and show associated MMR defects. Further, defects in MMR-related proteins MSH2 and PMS2 lead to resistance from alkylating agents (Hassen et al. 2016; Peltomäki 2016). Mutagens that cause damage to MMR proteins also impair various activities such as homologous

recombination, somatic hypermutation, immunoglobulin class switching, and trinucleotide repeats expansion (TNR). MMR mechanism is an important asset in maintaining the fidelity and integrity of DNA molecules; therefore, MMR-mediated DNA damage response can be an effective therapeutic target. A schematic representation is shown in Figure 5 about various DNA repair mechanisms activated during exposure to environmental mutagens (exogenous or endogenous mutagens).

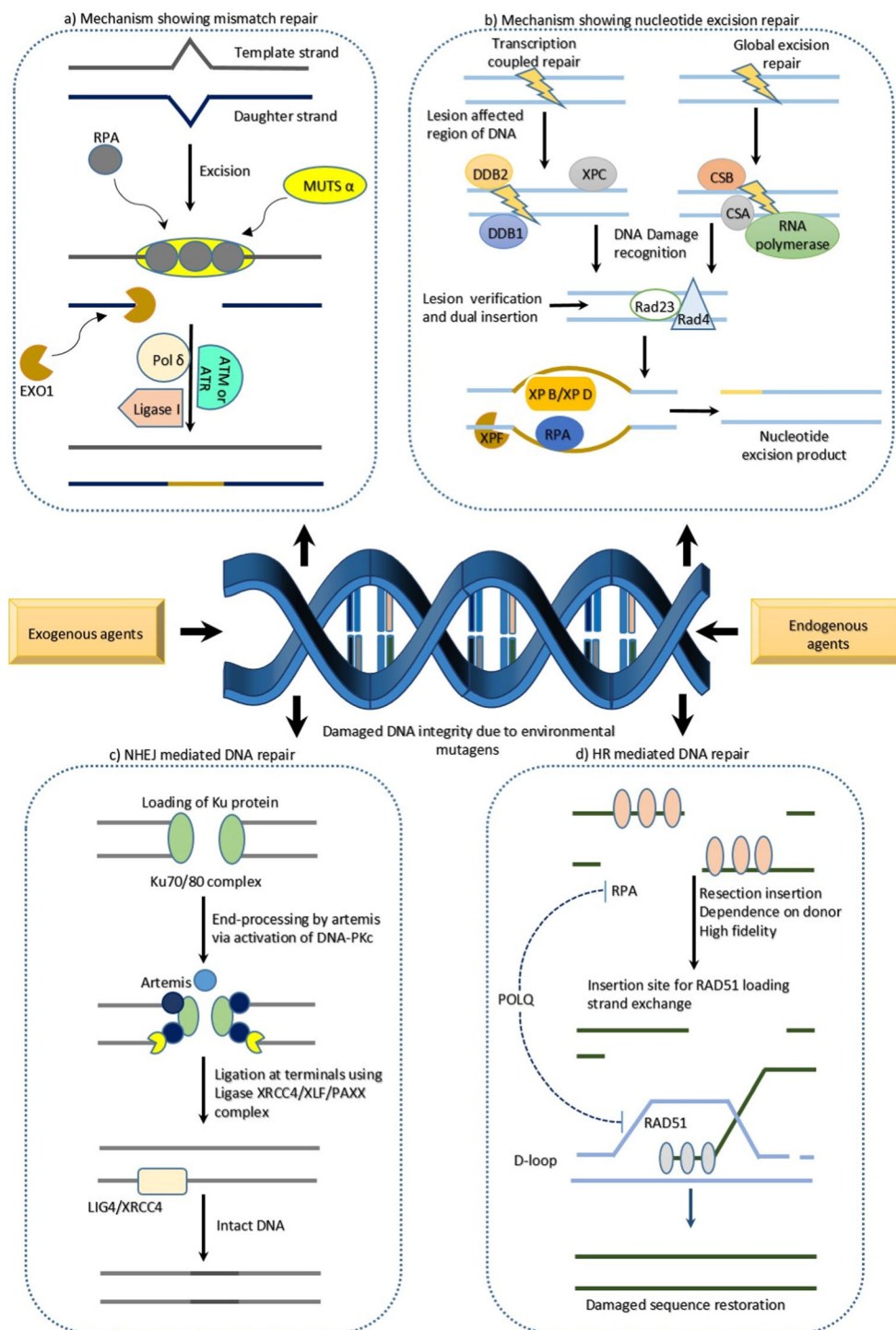
Nucleotide-excision repair mechanism in mammals and related signaling

Distortion in the helical structure of DNA by various lesions caused due to various environmental mutagens like exposure from UV irradiations and various chemical toxins is generally eliminated using nucleotide excision repair (NER) (Gillet and Schärer 2006). This repair mechanism plays a pivotal role in maintaining genomic integrity; therefore, defects in this repairment machinery led to the establishment of different cancers. Two major pathways that govern that induced as a result of UV-irradiation (Hart et al. 1978). NER is initiated by recognizing the affected site by DNA lesion, which is generally recognized by XP-related proteins (DDB2 and XPC). After successfully identifying lesions on the template strand, TFIIH and proteins such as s XPA come under action (Repair 2016). XPC-RAD23-CETN2 heterodimers are important in recognizing DNA lesions when discussing the GG-NER mechanism in mammals (Volker et al. 2001). GG-NER employs the XPC-RAD23-CETN2 heterodimer complex that plays a prominent role in the recognition of lesions that detects and binds to the DNA sites.

Fig. 5 Schematic representation of various DNA repair mechanisms activated during exposure to environmental mutagens that can be either exogenous or endogenous. **(a)** Mismatch repair mechanism. Lesion that arises on the template strand and excision occurs followed by the binding of various DNA-binding proteins (MUTS α), replication protein A (RPA). Recognition of the lesion and after excision, the machinery is taken up by exonuclease 1 (Exo1), Polymerase δ (Pol δ), ligase I, and ATM or ATR. These proteins then cause synthesis of the repaired base sequence. **(b)** Nucleotide excision repair that occurs either in a transcription-coupled manner and global excision repair. DNA binding proteins such as DDB2, XPC, and DDB1 bind for damage recognition, followed by loading of Rad23 and Rad4 proteins. Attachment of RPA protein then generates nucleotide excision product. **(c)** Non-homologous end joining (NHEJ) in which loading of Ku70/80 complex proteins occurs on the lesion affected region, carried forward by end-processing by the assembly of artemis and ligation of the processed region by Ligase XRCC4/XLF/PAXX proteins. These ligand proteins, after excision cause the synthesis of intact DNA. **(d)** Mechanism of homologous recombination after mutagenesis causes recognition of the lesion on the double-stranded DNA (dsDNA), attachment of the RPA protein to the lesion binding site preceded by insertion of RAD51 on the unwounded region. Formation of a D-loop occurs, and attachment of new repaired sequence within the D-loop causes successful synthesis of repaired DNA sequence

Further, the double helix is distorted, leading to the destabilization of bases (Min 2007). During the occurrence of indirect damage to the DNA, XPCs bind to the DNA region where there is a presence of mismatched bases and no presence of any lesions. To avoid any erroneous breakdown at the bases, GG-NER needs to verify that the existence of lesion at that particular binding region occurs, and to execute this step, DNA-dependent ATPase/helicase activity of TFIIH is required (Sugasawa et al.

2009). TFIIH is a complex assembly made up of two ATPase helicase subunits (XPD and XPB), from which XPB is required during NER and in the transcription mechanism (Oksenysh et al. 2009). XPD proteins, on the other hand, have dual activity (ATPase activity and a 5' to 3' helicase activity), important for NER but not required during transcription. Mutagens targeting and disrupting the sequence of nucleotides are taken care by the GG-NER pathway of DNA damage repair.



Genomic DNA is considerably larger, and the lesion's probability of occurrence is unexpectedly higher, causing an urgent need for a cell-free system. Assuming that there is a presence of a specialized mechanism assisting XPCs to identify lesions affected sites apart from whole naked DNA, different mechanisms are proposed. One such mechanism employs UV-damaged DNA damage binding protein complexes (UV-DDB). UV-DDB is known to be the assembly of DDB1 and DDB2, shows strong binding affinity and specificity to UV-damaged DNA (Fujiwara et al. 1999). These factors presumably bind to the pyrimidine photoproducts, attaching directly to the photolesions induced by UV and encounters for the presence of any lesion. But the base adducts that are bulky in nature, formed by chemical mutagens, are known to be the poor substrates for these UV-DDBs (Joon Hwang et al. 1999). Hence, UV-DDB repair mechanisms act to be more preferred when talking about the CPDs due to the poor recognition capability of XPCs. Mutagens that are crucial and cause these types of DNA damage, majorly photolesion due to exposure to radiations of ionizing origin, NER acts to be the line of defense and comes into roleplay as soon as a lesion is detected. Therefore, NER is an important repair mechanism in handling these types of lesions, and from the therapeutic prospect can be traced when talking photolesion induced DNA damage caused due to environmental mutagens.

DNA- DSB repair and related signaling cascades:

DSBs induced in DNA as a result of exposure from environmental mutagens such as the use of radiomimetic medicines such as neocarzinostatin and bleomycin, ionizing radiations (IR), use of cytotoxic agents such as camptothecin, doxorubicin, and etoposide appears to be the most lethal form of DNA damage (Helleday et al. 2007). This class of DSBs is known to be biologically important in nature as repairment of this defect is extremely crucial compared to any other DNA damage (Ciccio et al. 2010). The mechanism that holds the repair machinery of DSBs is carried either by homologous recombination, which occurs during the G2 and S-phase of cell cycle, or by NHEJ that can happen during any phase of the cell cycle (Karanam et al. 2012). For efficient regulation and in the maintenance of genomic instability, a series of signaling cascades get activated during DSB (Huang et al. 1996). If the DNA damage is severe in the cellular machinery, then activation of The DNA damage response occurs, which includes activation of cell cycle checkpoint, DNA repair, or regulation at the transcriptional level, ultimately leading to apoptosis (Bao 2011; De Zio et al. 2013). DNA DSBs, if not considered for corrections at the right time, lead to the loss of chromosomal regions and chromosomal translocations, thereby causing tumorigenesis due to genetic fusion or due to functional alterations in proto-oncogenes (Nikiforova et al. 2000). Studies convicting the role of these chromosomal arrangements include cancer of lymphatic origin and various non-lymphatic cancers (Richardson and Jasin 2000). NHEJ acts to be

the simplest form of DSB repair pathway, works by joining the two ends of DNA in a sequence-independent manner, and is the preferable form of repair in case of blunt ends, although sequence alteration may occur at breakpoints due to incompatibility. Proteins acting as the core of this machinery are DNA-dependent protein kinases and XRCC4/ligase IV/XLF complex (van Heemst et al. 2004). A ring-shaped heterodimer (Ku70/80) binds to this protein kinase, thereby binding to the ends of the DNA molecules (Weterings and van Gen 2004). This Ku-XRCC4-DNA ligase IV complex efficiently reconstituted the blunt ends through the NHEJ pathway. A large fraction of DSBs induced by different mutagens is repaired by homology-directed recombination-mediated repair (HRR). The process starts with resection of 5' DNA ends catalyzed by a trimeric complex MRN comprising of MRE11, RAD50, and Xrs/NBS1. The process is assisted by endonuclease Sae2/Ctp1/CtIP (Mimitou and Symington 2009). Further resection is carried out by single-strand endonuclease DNA2 or EXO, combined with Sgs1/BLM helicase. The next step is the formation of ssDNA binding protein RPA-RAD51 recombinase with 3' single-strand DNA filament. The mechanism is characterized by the synthesis of specific "double Holiday junctions" where the nicks are sealed by DNA ligase (Chang et al. 2017). An alternative pathway for DSB repair is alternative (microhomology-mediated) end-joining (alt-EJ/MMEJ). The pathway initiates with resection of 5' ends flanking DSB, followed by DNA end synapsis induced by PARP1. The polymerization is carried out by DNA polymerase θ (Pol θ), while the DNA ligase III -XRCC1 complex is required for the final ligation step (Cannan and Pederson 2016).

A comprehensive investigation of DDR gene alterations across 33 cancer types has revealed that HR is the most frequently mutated repair pathway, while a few cancers are associated with alteration in the NHEJ pathway (Knijnenburg et al. 2018). Mutational signatures affecting BRCA1, BRCA2, RAD51 genes (RAD51B, RAD51C), and BLM are found to be associated with HR alterations in cancers. A study in solid tumors has revealed the potential of HRD-targeted therapies as HR-DDR mutations were seen in 17.4% of tumors (Heeke et al. 2018). Likewise, a study has identified the role of MRE11 gene mutations in primary tumors. The gene is involved in DSB repair through NHEJ and HR pathways, and three different missense mutations are found to be associated with tumor development (Fukuda et al. 2001). As the failure of DDR in response to DSBs triggers tumor development, therapeutics targeting the DSB repair pathway could provide new treatment opportunities for a wide range of cancers.

Therapeutics avenues targeting cancer provoked by mutagens

Environmental mutagens cause cancer in humans. A plethora of studies have been performed to discover treatment avenues

for targeting cancer from therapeutics and prevention perspectives. Different areas have already been exploring, and still, new areas are being studied to expand current knowledge related to cancer. Recent innovations are focused on immune checkpoint inhibitor biologics, therapeutic vaccines, small drugs, and CAR-T cell injections (Alard et al. 2020). Different drugs like NSAIDs have been repurposed for the prevention and treatment of cancer (Zhang et al. 2018b; Turanli et al. 2018). On similar notes, infectious agents are also significant causes of causing cancer. To target cancer due to viruses and bacteria, anti-viral therapies are being discovered and used in clinics. In addition to therapeutics drugs, indicative of cancer disease and reason for cause is also essential. To understand this, the importance of biomarkers study is necessary to respect diagnostic, prognostic, and predictive cancer and its treatment (Califf 2018). Biomarkers related to DNA repairs have been explained in detail in this section.

Inhibitor targeting DNA damage caused due to environmental mutagens

The DNA damage response entails an orchestrated network signaling molecules and proteins involved in cell cycle arrest and repair mechanism. These are crucial for cell viability and avoid an accumulation of damaged DNA from one generation to another. In cancer, these responses are dysregulated, leading to either upregulation, downregulation, or loss of some other pathways and cause DNA damage, leading to cellular responses like inducing apoptosis and modulating cell cycle progression (Gavande et al. 2016). These pathways, being upregulated, can potentially be resistant to anticancer DNA damaging agents. Hence, key component inhibitors of the pathway being dysregulated are plausible to prevent this therapeutic resistance (Curtin 2013). Also, from a pharmacological aspect, the repair system's inhibition promises to enhance the cytotoxicity of a varied range of anticancer agents.

Moreover, defects in DNA damage responses are dependent on the complex pathways, the inhibition of which will initiate tumor-specific cell killing. Therefore, inhibitors targeting DNA damage can enhance the efficacy of chemotherapy as well as ionizing radiotherapy involved in DNA damage. Additionally, studies suggest that chemical inhibitors developed to exploit synthetic lethal interaction effectively and can pave the path for promising DNA repair targeted agents to be used in cancer therapy (Madhusudan and Hickson 2005). ROS generation commonly causes damage to nucleobases, spontaneous deamination, and aberrant methylation due to S-adenosyl methionine and methyltransferase enzyme activity. To repair this methylguanine DNA methyltransferase (MGMT) and prevents cell death caused by alkylating agents (Pegg 1990), many approaches have been worked upon to block MGMT using alkylating agents like temozolomide DTIC (dacarbazine), using pseudosubstrates

[e.g., O6-benzylamine (O6-BG) (Dolan et al. 1990). Some have been futile to show any considerable activity in cancer patients and have not progressed clinical trials any further (Khan et al. 2008; Kefford et al. 2009).

The repair mechanism involved could vary depending on nature. For instance, the extent of damage, for instance, nucleobase damages, is frequently repaired by BER, resulting in removing the damaged base and further repairing SSBs single-strand break repair (SSBR) pathway. Many studies have suggested that Methoxyamine, a small molecule, potentiates cytotoxicity as it binds to AP sites and targets BER. This further impact and prevent APE1 processing. APE1 increases tumor resistance while treating with chemotherapeutic agents, making it a key target for cancer therapy (Abbotts et al. 2014). The next class involves PARP inhibitors which include PARPi are NU 1025, NU 1064, AG 14361, AG 14699, GPI 15427, they have shown to decrease the repair mechanism of SSBs and survival too after being exposed to DNA methylating agents (Durkacz et al. 1980; Madhusudan and Hickson 2005). Thus, preclinical studies have potentiated DNA methylating agents' antitumor activity (Madhusudan et al. 2005). Moreover, some FDA has approved drugs that also act as PARPi in treatments, like ovarian cancer, which can be treated using Olaparib, Niraparib, and other combinations (LaFargue et al. 2019). These PARPi not only inhibit proteins involved in various pathways but also increase tumor-killing abilities. On the other hand, some pathways are in the development phase, like nonhomologous end-joining inhibitors, among which phosphoinositide-3-kinase related protein kinases (DNA-PKcs) have the most promising candidature. They undergo rough complex autophosphorylations and govern DNA interaction with proteins involved in repairs like cAbl, HSP90, PARP1, and H2AX, protect telomere (Zhou et al. 2013). The overexpression of DNA-PKcs is associated with radio-resistance in various carcinomas such as lung, esophageal, oral squamous cell, and other carcinomas (Srivastava et al. 2012), signifying that the chemical inhibition of DNA-PK can boost homologous recombination. The molecules belonging to this class are NU7026 [2-(morpholin-4-yl)-benzo[h]chromen-4-one]; NU7441; IC87102 (Willmore et al. 2004; Mohiuddin and Kang 2019). Some of the other emerging targets involve Pentamidine (Chow et al. 2004), antisense RNA targeting the ERCC1 protein (Selvakumaran et al. 2003), FA proteins (Ferrer et al. 2004), small inhibitory RNA molecules (siRNAs), but the long-term safety of these still need to be proven. Thus, as mentioned above, be it inhibitor or modulator of DNA repair can target a broad range of interactions, thereby presenting a new scope for escalating therapeutics for cancer (Table 2).

DNA damage and repair biomarkers in cancer therapy

The DDR system encompasses eight pathways: MMR, BER, checkpoint factors, Fanconi anemia, HRR, NER; non-homologous end-joining; and DNA translesion synthesis.

Table 2 Common environmental agents that are potent carcinogens

Mutagen	Source of contamination	Class of carcinogen	Mechanism of action	Damage caused	Type of mutation
Physical mutagens (heavy metals)					
Arsenic (As)	From contaminated food or water, industrial processes, consumption of alcoholic beverages	Group I carcinogen	Epigenetic Induction; DNA damage signaling; gene amplification, DNA repair inhibition	Mutates tumor suppressor genes, alter histones, cause DNA methylation	Causes aneuploidy, deletions
Cadmium (Cd)	Industrial processes causing occupational contamination through tobacco consumption, consumption of alcoholic beverages	Group I carcinogen	Induction of ROS; inhibition of DNA repair; promoting apoptosis	Build-up of oxidative stress, overexpression of oncogenic proteins, DNA methylation	Causes deletions at multiple loci in genes involved in DNA repair
Chromium (Cr)	Burning of coal, petroleum, fertilizer usage	Group I carcinogen	Generates free radicals, form adducts like DNA-protein crosslinks	Radicals affect transcriptions factor like metallothionein, inactivate DNA mismatch repair, tissue injury, inflammation	Cause transversion mutations, mainly G→T
Lead (Pb)	Using lead-based paints, leaded gasoline, or through other industrial processes	Group II carcinogen (inorganic lead) Group III human carcinogen (organic lead)	Free radical generation, disrupt transcription processes by replacing zinc in certain regulatory proteins	ROS induce promutagenic damage in DNA, including base modifications and SSBs and DSBs, adduct formation, interferes with the spindle fibers of dividing cells	Cause weak thymidine kinase (TK) or HGPRT mutations are observed
Nickel (Ni)	Exposure to nickel includes air, water, smoking tobacco, workers involved in the smelting process	Group I human carcinogen (Nickel compound) Group IIA as well as Group IIB carcinogen (Nickel in alloys)	Regulate expression of specific long non-coding RNAs, certain mRNA, and microRNA; upregulates HIF-1 α ; increase ROS accumulation, elevate 8-hydroxy-2'-deoxyguanosine	Form Ni-nucleic acid histone complexes which interfere with DNA, SSB, and DNA intrastrand cross-linking, suppress DNA damage-repair systems genes	Loss of expression of tumor-suppressor genes; gene silencing is observed
Chemical mutagens					
Naphthalene (simplest member of polycyclic aromatic hydrocarbons) and its derivatives	Major pollutant found in refining and petroleum, or asphalt industries, creosote production. Humans are also exposed to cigarette smoking, use of moth-repellent	Group 2B carcinogen	Naphthalene (Nph), metabolites undergo chemical reactions like isomerization epoxidation, substitution to form derivatives	These modified compounds react with DNA to form depurination adducts which lead to mutagenic effects	Causes DNA fragmentation, chromosomal aberrations, gene mutations, recombination abnormalities
Shale oils and mineral oils (contain Polycyclic aromatic hydrocarbons)	Present in lubricants, sprays, paint, Refinery industry	2-Naphthyl-amine (isomeric aminonaphthalenes) belongs to Group I carcinogen	N-Hydroxylation Activates the Metabolism Of 2-Naphthylamine form ROS that bind with DNA to form Adduct	Cause oxidative damage at bases in order T > C > G residues	Causes frameshift mutation, C→T transitions
Estradiol	Generally, by taking oral contraceptives or hormone therapy	Group I carcinogen	Involved in oxidative induction of cytochrome P450, metabolic activation and redox cycling of quinones	Causes DNA adduct formation, and some PAHs bind to cellular proteins and DNA, thereby causing cell disruption, tumors mutations, cancer	Cause insertional hypermutations by causing conversion of proto-oncogenes to oncogenes
Erionite	People working at construction sites (occupational exposure)	Group I carcinogen	Promotes cell proliferation which leads to fixation of genetic mutations	Causes error-prone DNA replication and interferes with DNA repair machinery	Germline mutation which leads to a malignant phenotype
Asbestos	People working in mining and milling industries (occupational exposure)	Group I carcinogen	Macrophages internalize Erionite and produce ROS which contributes to carcinogenicity The asbestos fibers lead to inflammation and cause genetic alterations, 8-OHdG formation, all of these lead to the growth of cancer	Damage gene transcription, DNA repair response Damage DNA directly by binding or by producing ROS, all these lead to lung overload	Mutations in BAP1 germline and <i>Nf2</i> Aneuploidy, structural changes in chromosomes at meta-and anaphase, the dominance of G→T transversions
Carcinogenic agents present in food items and drinks					
Acetaldehydes		Group I carcinogen			

Table 2 (continued)

	Humans are exposed to it by consuming alcoholic beverages		Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH) and binds to DNA	Produces ROS that may lead to lipid peroxidation and mutagenic adducts	Causes DNA hypomethylation, which regulates the expression of oncogenes and tumor-suppressor genes Causes mainly G:C→A:T transitions, and mutates Kras2 gene endogenously
Ethyl carbamate		Group 2A carcinogen	Ethyl carbamate oxidizes to the electrophilic vinyl carbamate epoxide, which reacts with the DNA	Interaction of the epoxide leads to the formation of DNA adducts, such as 1,N(6)-ethenodeoxyadenosine and 1,N(4)-ethenodeoxycytidine	
Aflatoxins	Contaminated food products	Group I carcinogen	Deteriorates the cell cycle checkpoint activation at the G2/M checkpoint site, forms reactive genotoxic intermediates, such as Aflatoxin-nucleic acid adduct (AFB-N7-Gua)	Mutates tumor suppressor gene, DNA strand breakage, DNA base damage, oxidative damage	Causes G → T transversion mostly, <i>Tp53</i> gene mutations are also observed
Red meat & processed meat	Consuming non-veg food items	Group 2A carcinogen & group I carcinogen	Increases N-nitrosation, oxidative load as well as lipid peroxidation product which impact of DNA repair, leads to inflammatory responses	Cause DNA breaks, adduct formation, the proliferation of cells,	Mutations in APC or β-catenin
Radiations					
UV radiation	Sunlight	Group I carcinogen	Excitation of oxygen to singlet oxygen; interaction of UV light with bases	Causes pyrimidine dimer formation, DNA base crosslinking, SSBs, oxidative damage	Causes missense, or nonsense mutations
Gamma rays	Uranium ore mining and fuel processing, nuclear energy, nuclear weapons, combustion of coal	Group I carcinogen	Direct interaction of radioactive particle with DNA sugars and bases	It can cause breaks in DNA, oxidizes bases, create abasic sites	Causes small deletions, single nucleotide base substitutions
X-rays	X-ray machines, food irradiation, airport security scanners	Group I carcinogen	Forms oxyradicals, excites oxygen to singlet oxygen	This leads to DSBs, deletion, insertion, oxidative damage	Causes chromosomal rearrangements and deletions
Infectious agents					
<i>Helicobacter pylori</i>	Through fecal contamination, physical contact (through oral means/mouth)	Group I carcinogen	Causes inflammation predisposes cells in the stomach lining to become cancerous	Causes inflammation which releases ROS and 8-hydroxy-2'-deoxyguanine (8HdG)	Mostly transversion mutations like AT → CG and GC → TA
<i>Salmonella typhi</i>	Through contaminated food and unhygienic conditions	–	Produces toxin of CDT group, which activates an irreversible cell cycle arrest and apoptosis	CDT induce DSBs, lesions which speculated to cause DNA damage leading to cancer progression	Deletions at chromosomal regions harboring tumor suppressor genes, frequent <i>KRAS</i> mutation
<i>Streptococcus bovis</i> (type I, now known as <i>Streptococcus gallolyticus</i>)	Through unhygienic conditions (like coming in contact with animal wastes)	–	Enhanced phosphorylation of MAPK, activate Wnt pathway, modulates the bile acid apical transporter gene <i>Slc10A2</i> , promotes neoplastic lesions resulting in cancer	Stimulates uncontrolled proliferation, causes inflammation-induced tumor progression, forms abnormal crypts	Mutations affecting the APC-KRAS-p53 pathway are known to trigger neoplastic transformation
<i>Chlamydia trachomatis</i>	Transmitted through sexual contact	–	Causes pelvic inflammation which becomes secondary predisposition for cervical cancer	Interferes with DNA repair machinery	(as it is only speculated to increase risk of cervical cancer)
<i>Clonorchis sinensis</i>	Through contaminated food and unhygienic conditions	Group I carcinogen	Triggering NF-κB-mediated inflammation produces ROS, disturb host redox homeostasis	Forms mutagenic DNA adducts, DNA lesions, impair DNA repair system, increase cell proliferation	Causes DNA base-pair substitution mutations and genome instability
Colibactin (a genotoxin produced by <i>Escherichia coli</i> strains)	Through contaminated food and unhygienic conditions	–	Alkylates DNA causes cell cycle arrest, genotoxicity, and senescence	Forms unstable colibactin-DNA adduct, leads to DNA DSBs	Mutates oncogenes or tumor suppressor genes, <i>APC</i> genes contributing to tumorigenesis
Hypoxia	Natural and simulated altitudes are prime contributors	–	Stimulates a complex cell signaling network like HIF, PI3K, MAPK, and Nfkb pathways,	Defective DNA repair, unrepaired DSBs, error-prone replication	Increased point mutations, transversion mutations are seen

Table 2 (continued)

	Cancer	Medications	References
Chemotherapeutic drugs			
Temozolomide (alkylating agent)	Group II carcinogen	It converts to MITC (reactive compound at physiological Ph). The cytotoxicity effect of MITC primarily due to the alkylation of guanine at the O6 and N7 in DNA. Generally, it binds to the n7 reactive center on the purine base forming crosslinks	Results in DNA lesions form O ⁶ -methylguanine adducts
Cisplatin (alkylating agent)	Group IIA carcinogen		Some hypermutations lead to mispairing of O ⁶ -meG with thymine instead of guanine to cytosine. Short insertions and deletions at putative crosslinked strands
Mutagen			
Physical mutagens (heavy metals)			
Arsenic (As)	Lung cancer	Sulforaphane, metal chelators, alpha-lipoic acid	(Faita et al. 2013; Lau et al. 2013; Rao et al. 2017; Wei et al. 2019)
Cadmium (Cd)	Skin Cancer	5-FU, 5% imiquimod	(Guha Mazumder et al. 2001; Khandpur and Sharma 2003; Yu et al. 2006)
	Lung cancer	2,3-dimercapto-1-propanesulfate	(Tandon et al. 2002; Luevano and Damodaran 2014)(DesMarais and Costa 2019)
	Renal cancer	N-acetylcysteine, 2, 3-dimercapto-1-propane sulfonic acid	(Flora et al. 2008; Rafati Rahimzadeh et al. 2017)
	Breast cancer	Ethylene diaminetetraacetic acid (EDTA), vitamin C, vitamin E	(DePasquale 1999; Asara et al. 2012; Luevano and Damodaran 2014)
	Pancreatic cancer	Fluoropyrimidines, especially 5-fluorouracil (5-FU)	(Zhai et al. 2015; Chen et al. 2015)
	Prostate cancer	Dietary supplies rich in zinc, magnesium, iron have been known to be effective to cure	(GUNN et al. 1963; Pal et al. 2017)
Chromium (Cr)	Lung cancer	Psoralidin (Pso), zinc	(Feng et al. 2003; Holmes et al. 2008; M. Urbano et al. 2012; Wang et al. 2017; DesMarais and Costa 2019)
Lead (Pb)	Renal adenocarcinoma	Quercetin, propylthiouracil, green tea polyphenol extracts, vitamin C	(Johnson 1998; Silbergeld 2003; Hartwig 2013; Zhang et al. 2014; Zhai et al. 2015)
Nickel (Ni)	Lymphoblastic Leukemia	Penicillamine (DPA)	(Costa and Klein 1999; Gopal et al. 2009; Guo et al. 2019)
Chemical mutagens	Breast cancer	Calcium disodium versenate	(Crimmon and Tran 2010; Guo et al. 2019)
	Lung cancer	Meso-2,3-dimercapto-succinic acid (DMSA)	(Jeffrey Lewis 2012; Clergé et al. 2021)
Naphthalene and its derivatives	Cancer-related to urinary bladder	Using anticancer drugs suppress the genotoxic effects	(Vineis and Pirastu 1997; Besaratinia et al. 2002; Ohnishi et al. 2002; Gulina 2020)
	Shale oils	Combined use of Methotrexate, Adriamycin, and Cisplatin	
Polycyclic aromatic hydrocarbons	Skin cancer	Hydroretreatment, solvent extraction (reduce the PAH content)	(Watson et al. 1985; Baan et al. 2009; Rastogi et al. 2010)
	Estradiol	Endometrial cancer	
Erionite	Mesothelioma	Tamoxifen, Progesterin	(Henderson and Feigelson 2000; Hammond and Soules 2009; Gulina 2020)
Asbestos	Mesothelioma	ALIMTA + Cisplatin + Mitomycin C	(Tansan et al. 1994; Calvert et al. 2000; Peake 2009; Demiret et al. 2015; Ortega-Guerrero et al. 2015)
	Lung cancer	Ifosfamide + Interferon- α Carboplatin + Paclitaxel Cisplatin Pemetrexed Only palliative care is possible using nerve blocks, non-steroidal anti-inflammatory analgesics	(Vogelzang et al. 2003; Musk et al. 2011)
Carcinogenic agents present in food items and drinks			
Acetaldehydes	Malignant esophageal tumor	Cisplatin-based drugs like carboplatin, oxaliplatin are commonly recommended along with radiation therapy	(Pflaum et al. 2016; Matejic et al. 2017)
Ethyl carbamate	Lung cancer	Garlic derivative diallyl sulfone, temozolomide (TMZ) loaded into gold nanoparticles or TMZ present inside liposomes	(Huang et al. 2011; Järnholm and Aström 2014; Musk et al. 2020)

Table 2 (continued)

Aflatoxins	Hepatocellular carcinoma	Oltipraz (4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione), chlorophyllin, broccoli sprout extract	(Hernandez and Forkert 2009; Forkert 2010; Pflaum et al. 2016; Hamzawy et al. 2017)
Red meat & processed meat	CRC; postmenopausal breast cancer; lung, esophageal and gastric malignancies	Under current investigation	(Jackson and Groopman 1999; Wild and Montessano 2009; Hamid et al. 2013) (Lichtenborg et al. 2005; Domingo and Nadal 2017)
Radiations			
UV radiation	Melanoma	Imiquimod, Doxil, Nab-paclitaxel	(Brodell and Yasmeen 2013; Orthaber et al. 2017; Laikova et al. 2019)
Gamma rays	Skin cancer	Melatonin	(Sudprasert et al. 2006; Shabeeb et al. 2019)
X-rays	Thyroid cancer	Cabozantinib, Sorafenib, Lenvatinib, Vandetanib,	(Zhang et al. 2015b; Albi et al. 2017; Kim and Han 2019)
	Breast cancer	Trastuzumab, N-acetylcysteine, sodium ascorbate, alpha-lipoic acid	(Liang et al. 2003; Kuefner et al. 2012)
	Lung cancer	Dichloroacetate	(Bonnet et al. 2007; Tan Allen et al. 2015)
Infectious agents	Gastric cancer	Gaflac, Amoxicillin, Tetracycline	(Ultrasound et al. 2004; Chang and Parsommet 2010; Ma et al. 2012)
<i>Helicobacter pylori</i>	Gallbladder Cancer	Ampicillin, Cisplatin, Gemcitabine,	(Tewari et al. 2010; Fais et al. 2016; Di Domenico et al. 2017; Mi et al. 2019)
	CRC	Capecitabine, Fluorouracil (5-FU) Irinotecan, Oxaliplatin	(Burns et al. 1985; Ahmed et al. 2011; Abeni et al. 2013; Inanc et al. 2014; Agnes et al. 2021)
<i>Streptococcus bovis</i> (type I, now known as <i>Streptococcus gallolyticus</i>)	Cervical cancer	–	(Smith et al. 2002a; Karim et al. 2018)
<i>Chlamydia trachomatis</i>	Cholangiocarcinoma (CCA)	(as an association is not definitive)	(Choi et al. 2004; Maeng et al. 2016; Kim et al. 2016)
<i>Clonorchis sinensis</i>	Colorectal Cancer (CCR)	At present, there is no effective adjuvant therapy, only surgical resection is hope for long-term survival. Followed by Radiation therapy postoperatively	(Dalmasso et al. 2015; Wilson et al. 2019; Dziubanska-Kusibab et al. 2020)
Colibactin (a genotoxin produced by <i>Escherichia coli</i> strains)	Bladder, brain, breast, cervix, CRC, endometrium, pancreas cancer	Colibactin-inhibiting drugs, adjuvant therapy, chemo-drugs, and surgery	(Koi and Boland 2011; Wilson and Hay 2011; Muz et al. 2015; Semenza 2017)
Hypoxia	Acute myeloid leukemia (AML), Acute lymphoblastic leukemia (ALL)	Hypoxia activated prodrugs like TH-302, Cisplatin, Chlorambucil, Veliparib	(Ogura et al. 2011; Zhang et al. 2012; Momota et al. 2013; Choi et al. 2018; Daniel et al. 2019)
Chemotherapeutic drugs	Secondary tumor in Hodgkin's Lymphoma, secondary leukemia	Close follow is needed.	(Pedersen-Bjergaard et al. 1991; Greene 1992; Dasari and Tchounwou 2014; Muggia et al. 2015; Szikriszt et al. 2016)
Temozolomide (alkylating agent)		Close follow is needed.	
Cisplatin (alkylating agent)		Close follow is needed.	

Defects in these pathways lead to genomic instability and hence cancer (Das et al. 2021). Scarbrough et al. identified three susceptibility DNA repair genes, RAD51B, MSH5, and BRCA2, and pleiotropic association of DNA repair mechanism with lung, ovary, prostate, breast, and colorectal cancer (Scarbrough et al. 2016). Research over the years has contributed substantially to our understanding of the importance of biomarkers as diagnostic, prognostic, and predictive markers regarding cancer and its treatment. More importantly, the generation of some biomarkers inside cells, namely micronuclei (MN), nucleoplasmic bridges (NPB), and nuclear buds (NPB), can be utilized as an indicator of DNA damage due to exposure to cytotoxic or DNA damaging agents or any other environmental carcinogens (Alhmoud et al. 2020). For early detection of DNA damage, diagnostic biomarkers including phosphorylated histone 2Ax (γ H2AX), 8-OHdG or 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) facilitation disease detection and prognosis. γ H2AX is proven to be one of the most promising markers for DSB in precision medicine (Ivashkevich et al. 2012; Reddig et al. 2018). Besides, γ H2AX foci levels have also been used as predictive markers where they predict the pathological complete response (pCR) in TNBC patients and cervical Cancer (Vici et al. 2015, 2016) and monitor cancer progression and treatment because therapeutic agents either induce DSBs directly (such as radiation, other environmental factors) or produce diverse DNA damage that causes DSBs formation (such as PARP inhibitors, gemcitabine, platinum drugs) (Sedelnikova and Bonner 2006). Evidence and understanding of DNA repair function and its correlation with drug response in individual tumors will be critical to patient selection for DNA repair targeted therapies.

Genomic and functional assays of DNA repair pathway activity are being explored extensively as potential prognostic or predictive biomarkers for targeted therapies. These biomarkers **consider** specific alterations in DDR pathways or genomic signatures resulting from the aberrant repair. For example, germline BRCA1 or BRCA2 (BRCA1/2) mutations (HRR deficiency) and somatic ERCC2 mutations (NER pathway) in epithelial ovarian cancer patients and urothelial cancer patients respectively enhance platinum drug sensitivity because it decreases the capacity to repair platinum-induced DNA damage (Van Allen et al. 2014; Mylavarapu et al. 2018; Palacios et al. 2020). On a similar note, HRR and BER deficiencies in cancer cells sensitize them to topoisomerase-I inhibitors (e.g., topotecan). In contrast, HRR and NHEJ deficiencies sensitize to topoisomerase-II inhibitors (e.g., doxorubicin and etoposide) (Maede et al. 2013). In addition, BRCA1/2 mutations (HRR deficiency) serve as an essential biomarker for PARP inhibitors' sensitivity (PARPi) response. PARPi is selectively lethal to HRR-deficient cells. Olaparib was the first FDA-approved drug for ovarian cancer with BRCA mutation (Farmer et al. 2005;

Matulonis et al. 2016; Golan et al. 2019). Aurora A, a mitotic kinase, is involved in cell cycle control and has been overexpressed in many cancers. Aurora A prevents RAD51 from being recruited to DNA DSBs via a process that requires the checkpoint kinase CHK1 to be inhibited. As a result, HR's DSB repair is hampered, and cells are more vulnerable to PARP inhibitors. More importantly, overexpression of Aurora A is a potential predictive biomarker of PARP inhibitor sensitivity (Michels et al. 2014).

Abundant published evidence suggested that alteration in tumor DNA repair can be the therapeutic target, and its deficiency is linked with clinical biomarkers (Li et al. 2021).S. For instance, the most excellent and well-characterized link allying specific DNA repair alteration and response to a DNA-damaging alkylating agent is the correlation between O⁶-methylguanine MGMT promoter methylation and response to temozolomide in glioblastoma multiforme (GBM) (Hegi et al. 2005). Recent studies using next-generation sequencing next-generation sequencing (NGS)-based methods to expand the association between specific DNA repair-deficient states and specific DNA-damaging agents (Nesic et al. 2018). For example, DNA adducts are created because of DNA-damaging agents (such as UV light and platinum chemotherapies) repairs by NER pathways that involve ERCC2 (DNA helicase). Research by Allen et al. and other groups showed that somatic ERCC2 missense mutations correspond to muscle-invasive bladder cancers (MIBC), and alteration (loss of function) in ERCC2 in tumors reveal improved sensitivity to cisplatin-based chemotherapy (Van Allen et al. 2014; Liu et al. 2016).

Moreover, defects in the DDR pathway have been studies concerning tumor immunogenicity as delayed repair can alter the tumor genome, which causes an imbalance in the immune system in the TME (Mouw et al. 2017). Wang et al. data allude that comutations (defined as co-mut+) in DDR pathways of homologous recombination repair and mismatch repair (HRR-MMR) or HRR and BER (HRR-BER) correlates with biomarkers (such as enhanced tumor mutational burden (TMB) and neo-antigen load (NAL) and greater levels of immune gene expression signatures) which all together predict the efficacy of ICB. Other biomarkers such as PD-L1 expression, high microsatellite instability also predict the response of ICB in patients with cancer (Wang et al. 2018; Zhang et al. 2020; Jiang et al. 2021). Also recently, new anti-cancer drugs have been produced that blocks the regulatory pathways governing the DDR response are (a) PARP inhibitors (e.g., Niraparib, Olaparib, Talazoparib, Rucaparib, Veliparib); (b) CHK1 Inhibitors (e.g., GDC-0575, MK-8776, Prexasertib, SRA-737); (c) ATR inhibitors (e.g., Ceralasertib, BAY1895344, Berzosertib, M4344); (d) ATM inhibitors (e.g., AZD0156, M3541); (e) DNA-PK inhibitors (e.g., AZD7648, CC-115, Nedisertib, M9831); (f) WEE1 inhibitor (e.g., Adavosertib) (Cleary et al. 2020).

Melanoma patients with BRCA2 mutation respond well to ICB (Lemery et al. 2017). Thus, DNA repair deficiency has been explored as biomarkers and also as therapeutic targets for understanding oncology. Further, in the future, NGS-based studies will continue to uncover links between DNA damage, biomarkers, DNA repair pathway function, and response to chemotherapeutics therapy. Table 3 describes DNA repair pathways and biomarkers in cancer.

Anti-viral therapy used in combating cancer

Human viruses have been extensively studied over the past 60 years and are responsible for 10–15% of the total world human cancer burden. According to International Agency for Research on Cancer (IARC), in 2002 (Parkin 2006) estimated total of infection-attributable cancer is 1.9 million (17.8% of the global cancer burden), and in 2018 approximate 2.2 million infection-attributable cancer cases were diagnosed worldwide (13% of global cancer incidence). Currently, eight viruses are known to cause chronic infection and also have been associated with cancer in humans, including DNA viruses: Hepatitis B virus (HBV), human papillomavirus (HPV), Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV) and Merkel cell polyomavirus (MCV) and the simian virus 40 (SV40) and RNA viruses: hepatitis C virus (HCV), human T cell lymphotropic virus type 1 (HTLV-1), (Shah 2007; de Martel et al. 2020; Rositch 2020). Data and results from different laboratories across globes have shown that viral load (a marker of virus replication activity in the human body) and cancer risk are often akin for virus-associated cancers, for example, HBV and HCV for hepatocellular carcinoma (HCC), EBV for nasopharyngeal carcinoma (NPC), HPV for cervical cancer, MCC for Merkel cell carcinoma and SV40 for brain cancer and mesothelioma, and non-Hodgkin's lymphoma (Vilchez and Butel 2004; Shih et al. 2014; Carbone et al. 2020). Each virus has a unique mechanism for promoting carcinogenesis and develops a tumor (Moore and Chang 2010). The viral factor of HPV, EBV, KSHV, SV40, HCV, and HTLV encodes oncoproteins that induce genomic instability by inactivating the p53 and retinoblastoma proteins (pRB), the two important regulators play a central role in the initiation of human cancers via both somatic and germline mutations (Levine 2009). Moreover, it also accumulates mutations, dysregulated cell cycle, DNA damage, and viral DNA integration into the human genome (Weitzman et al. 2010). Currently, anti-viral therapy, including therapeutic drugs and vaccines, immunotherapy, RNA –interference-based therapies, which have been applied on these seven viruses-associated cancers, have yielded promising results in cancer prevention and treatment (Table 4). Studies also support that viral infection also generates free radicals such as ROS and RNS, which induces oxidative and nitrative DNA damage that often occurs during inflammation can contribute

to carcinogenesis (Georgakilas et al. 2010; Chen et al. 2014). Increased concentration of ROS can directly influence NF- κ B activation. Hagen and colleagues demonstrated a connection between Oxidative stress, DNA damage with HCC (Hagen et al. 1994). Interestingly, Cerimele and co-workers showed increased ROS levels and altered NF- κ B activation in EBV-positive Burkitt's lymphoma cells compared to EBV-negative Burkitt's lymphoma cells (Cerimele et al. 2005).

Some viruses are known as oncolytic viruses that include both naturally occurring viruses and laboratory modified viruses. These viruses have been used directly to target and kill cancer cells. In addition, some of these viruses infect tumor cells and cause oncolysis producing and releasing new virus progeny to kill nearby tumor cells. It also releases tumor antigen (danger signals) like DAMPS and PAMPS, which will stimulate an immune response in the body against cancer by (a) activating and encouraging maturation of dendritic cells (DCs) in nearby TME by upregulating co-stimulatory markers, such as CD80, CD83, and CD86; (b) tumor antigens or debris processed by professional antigen processing cells (such as mature DC, macrophages, and B cells) which subsequent T cell priming; (c) activated B cells produces neutralizing antibodies, that tag with infected tumor cells for ADCC and phagocytosis by NK cells and M1 macrophage respectively; (d) direct killing of infected and non-infected tumor cells by CD8⁺ T cells and NK cells via releasing INF γ /GranzB and GranzB/Perforins in TME. In 2015, an oncolytic virus Talimogene laherparepvec (T-VEC; Imlygic®), a genetically engineered second-generation oncolytic herpes simplex virus type 1 (HSV-1), had been approved by FDA for treating the patient with melanoma (Fukuhara et al. 2016; U.S. Food and Drug Administration 2017). This works by infecting cancer cells to produce the immune-stimulating GM-CSF protein but does not infect healthy cells. Although many viruses are being evaluated as potential cancer treatments in clinical trials, only one has been approved to date (Hemminki et al. 2020). It appears anti-viral therapy, including oncolytic viruses, will be part of future multimodality approaches and data, yielding promising results in cancer prevention and treatment.

Anti-inflammatory nonsteroidal anti-inflammatory drugs as chemical cancer prevention

Inflammation is one among the hallmark of cancer (Hanahan and Weinberg 2011). Therefore, in recent years, extensive research has focused on using nonsteroidal anti-inflammatory drugs (NSAIDs) to target inflammation in cancer prevention and treatment (Wong 2019; Iovoli et al. 2020). Few examples of NSAIDs include ibuprofen, mefenamic acid, celecoxib, aspirin, valdecoxib, and diclofenac, have been used as cancer therapy. These drugs have the potential to block cyclooxygenase (COX) or prostaglandin endoperoxide H

Table 3 DNA repair pathways and associated biomarkers in cancer

S.No	DNA repair pathway	Indication	Criteria	Biomarker
1	O ⁶ -methylguanine-DNA methyltransferase (MGMT)	GBM	Damaged guanine nucleotides	MGMT promoter methylation enriched in CpG island methylator phenotype (G-CIMP) subtype
2	Mismatch repair (MMR)	Colorectal, Endometrial, Gastric, Ovarian, Prostate, Breast, Glioma	Germline mutations in DNA mismatch repair genes: MLH1, MSH2, MSH6 or PMS2	Increase TMB, increased NALs, MMR mutational signature, Increased expression of immune-related genes (PD-1, PD-L1, LAG3, CTLA-4)
3	Homologous recombination (HR)	Ovarian, Breast, Prostate Cancer	Germline mutations in BRCA1 or BRCA2	Transcriptomic HR deficiency (HRD) scores: HRD-LOH, HDR-TAI, HDR-LST, Increase TMB, Increased NAL, HR mutational signature, Upregulated cytotoxic T-cell gene signature
4	Polymerase (POLE/ POLD1) proofreading	Endometrial, Colorectal cancer	Germline mutations in POLD1 or POLE	A somatic point mutation in exonuclease domain of POLE or POLD1; POLE/POLD1 mutational signatures, Increased TMB
5	Nucleotide excision repair (NER)	Muscle-invasive Bladder tumors, Lung Cancer	Single nucleotide polymorphisms in ERCC1	Increased TMB, ERCC2-related mutational signature, Somatic mutation in ERCC2 or other NER gene(s)
6	Base excision repair (BER)	Colorectal cancer	Germline mutations in MUTYH	BER mutational signature, Biallelic MUTYH mutations

Table 4 Human cancer viruses and their associated cancers, and their specific anti-viral therapies

S.No	Virus	Genome type	Reported year	Indication	Antiviral therapy	Reference
1	HBV (DNA virus)	Single-stranded and double-stranded DNA	1965	HCC	Interferons based therapy (IFN- α , Pegylated IFN- α 2a) Nucleos(t)ide analogs based therapy(Lamivudine, Adefovir, Entecavir, Tenofovir, Telbivudine)	(Blumberg et al. 1965; Lai et al. 2006; Zhang et al. 2018a) (Papatheodoridis et al. 2015; Xie 2017)
2	HCV (RNA virus)	Hepadnaviridae Positive-strand, single-stranded RNA flavivirus	1989	HCC	Combination of Peg- IFN- α and Ribavirin Direct-acting antivirals (DAA) (Protease inhibitors oral agents: Boceprevir, Telaprevir)	(Choo et al. 1989; Harada et al. 2015) (Wilby et al. 2012; Falade-Nwulia et al. 2017; Lin et al. 2020)
3	EBV/HHV4 (DNA virus)	Double-stranded DNA herpesvirus	1964	PTLD, NPC, HL EBV-associate lymphoma	Immunotherapy (EBV-specific cytotoxic T cells, EBV-specific adoptive T cell Immunotherapy) Virus directed therapy (Combination of Lytic replication inducer agent and Acyclovir/Ganciclovir)	(Epstein et al. 1964; Gallot et al. 2014; Huang et al. 2017) (Meng et al. 2010)
4	HPV (DNA virus)	Double-stranded DNA Papillomavirus	1983	Cervical cancer	Therapeutic HPV vaccine (focus on HPV-16 and HPV18): vaccine targeting HPV E6 and E7 antigens - Viral-vector-based (i.e., vaccinia, adenovirus, alphavirus) - Bacterial-vector-based (i.e., Listeria, Salmonella, Lactococcus) - Protein or peptide-based (HPV E7 antagonist, E6-binding aptamer) - DNA or RNA or cell-based RNA-interference-based therapy (Antisense oligonucleotides, ribozymes (e.g., Anti-E6 ribozyme, and siRNAs) Zidovudine and IFN- α ; Zidovudine and IFN- α -2 β	(Durst et al. 1983; Hung et al. 2008; Lin et al. 2010) (Jung et al. 2015)
5	HTLV-1 (RNA virus)	Positive-strand, single-stranded RNA Retrovirus	1980	Acute and lymphoma ATLL		(Poiesz et al. 1980; White et al. 2001; Hodson et al. 2011; Kinpara et al. 2013)
6	KSHV/HHV8 (DNA virus)	Retrovirus	1994	AIDS-KS	Antiviral herpesvirus drug (Ganciclovir, Cidofovir, histamine receptors (HxRs) agonist)	(Carter 2021; Chang et al. 1994; Medveczky et al. 1997; Chen et al. 2019)

Table 4 (continued)

S.No	Virus	Genome type	Reported year	Indication	Antiviral therapy	Reference
		Double-stranded DNA herpesvirus			HAART, PI based-HAART, NNRTI based regime	(CSL STYLE ERROR: reference with no printed form.]; Bourboula et al. 2004; Bower et al. 2004; Uldrick and Whitby 2011)
				HIV-negative KS	HIV protease inhibitor (Indinavir)	(Gantt et al. 2011)
				KS	Anti-herpesvirus therapeutic agents - For latent KSHV infection: Allicin and Glycyrrhizic Acid; - For lytic KSHV infection: nucleoside analogs such as Acyclovir, Ganciclovir, Zidovudine, and Valganciclovir)	(Xie et al. 2020)
7	MCV (DNA virus)	Double-stranded DNA polyomavirus	2008	MCC	Interferon (IFN- α and IFN- β)	(Feng et al. 2008)
8	SV40 (DNA virus)	Polyomavirus of the rhesus macaque	1960	Mesothelioma, NHL, Brain tumor	Gene therapy; pyrrole-imidazole polyamides	(Sweet and Hilleman 1960; Strayer 1999; Butel 2012; Edwards and Fisher 2018; Carbone et al. 2020)

Table 5 Role of NSAIDs drug in cancer treatment and prevention

S.No.	NSAIDs drug	Target	Indication	Effects on cancer	Reference
1	Aspirin	COX-1 and COX-2	Gastric adenocarcinoma, CRC, breast cancer	<ul style="list-style-type: none"> • Downregulation of Bel-2 expression • Downregulation of MMP-2 expression prevents migration to ECM IN CRC • Impaired immune system's normal response (help cancer cells to hide). • Upregulation of hMLH1, hMSH2, hMSH6, and hPMS2 expression increase DNA mismatch repair (MMR) proteins via COX-independent mechanisms, results in apoptosis. • Upregulation of XRCC3 expression • Overcome drug resistance against Cisplatin, 5FU. • Induces apoptosis via a caspase-3 pathway 	(Goel et al. 2003; Chen et al. 2005; Leung et al. 2008; Nicholl 2010; Zelenay et al. 2015)
2	Mefenamic acid	COX-1 and COX-2	Liver cancer	<ul style="list-style-type: none"> • Inhibits inflammation-related stemness gene expression (especially ICAM3) • Decreased HDACs and histone demethylase (KDM6A/B) expression that mediates histone acetylation and methylation and suppresses gene expression via a COX2-dependent way • Block constitutive activation of NF-κB and IKKα prostate cancer • In combination with esculetin, it reduces tumor cell growth. • In combination with carboplatin, reduce tumor cell proliferation (synergistic effect) 	(Ho Woo et al. 2004; Shiiba et al. 2017)
3	Ibuprofen	COX-1 and COX-2	Prostate cancer	<ul style="list-style-type: none"> • Hamper cancer cell migration through attenuation of cellular calcium mobilization • Suppress angiogenesis via reducing VEGF expression. 	(Andrews et al. 2002; Palayoor et al. 1999; Shen et al. 2020)
4	Piroxicam	COX-1 and COX-2	Bladder cancer, Breast cancer, Skin cancer	<ul style="list-style-type: none"> • Degradation of anti-apoptotic Bel-XL • Act as immunomodulatory. • Activation of pro-apoptotic Bax • Downregulates Sp transcription factors and Sp-regulated genes (include survivin, bel-2, EGFR, cyclin D1, p65 subunit of NFκB and VEGF) • induced ROS and decreased microRNA-27a levels in CRC • Decreased M2 macrophages recruitment, cancer-related inflammation, and angiogenesis 	(Noguchi et al. 1995; Mohammed et al. 2002; Campione et al. 2015; SILVA et al. 2017)
5	Indomethacin	COX-1 and COX-2	CRC, Gastrointestinal Cancer	<ul style="list-style-type: none"> • Synergistic effect of combination lumiracoxib and docetaxel (better efficacy) • Selective COX-2 inhibitor induces apoptosis • Nanoparticle (CKGPEC stabilized etoricoxib) showed improved efficacy in CRC. • Concurrent addition etoricoxib improves chemo-radiation combination in cervical cancer 	(Wang and Zhang 2005; Guo et al. 2013)
6	Sulindac acid	COX-1 and COX-2	CRC, breast cancer	<ul style="list-style-type: none"> • In combination with Gefitinib showed better efficacy in NSCLC. (EGFR increases COX-2 expression) • Induces cell cycle arrest by decreasing cyclin D1/PRAD1 expression and increasing expression cell cycle arrest genes, including p21/WAF1, p33/ING, GADD34, and GADD45. 	(Bank et al. 2008; Li et al. 2015; Yin et al. 2016; Sui et al. 2018)
7	Lumiracoxib	COX-2	NSCLC		(Hao et al. 2008; Emam Kassab 2019)
8	Etoricoxib	COX-2	Cervical cancer, CRC		(Sharma et al. 2010; Dhar et al. 2020; Malviya et al. 2020)
9	Rofecoxib	COX-2	CRC, pancreatic cancer, NSCLC		(Tseng et al. 2002; Byrne et al. 2007; Midgley et al. 2010; Buzharevski et al. 2020)

Table 5 (continued)

S.No.	NSAIDs drug	Target	Indication	Effects on cancer	Reference
10	Celecoxib	COX-2	Breast cancer, CRC, lung, prostate, stomach, head, and neck, gastric cancer	<ul style="list-style-type: none"> • Carborane-containing derivatives of rofecoxib showed improved efficacy in melanoma and CRC • Increase p53 gene expression through upregulation of PUMA • Activation of tumor suppressor miR-29c induced suppression of Mcl-1 and apoptosis in gastric cancer. 	(Arun et al. 2001; Lai et al. 2008; Liu et al. 2008; Saito et al. 2013; Toloczko-Iwaniuk et al. 2018; Saxena et al. 2020)
11	Diclofenac	COX-2	CRC, neuroblastoma, ovarian, cervical and pancreatic cancer	<ul style="list-style-type: none"> • Inhibit Wnt/β-catenin signaling via the activation of NF-κB in CRC • Downregulates PI3-K/Akt/PTEN pathway, increase ROS production, induces apoptosis in CRC. • Generate arginase activity in the tumor stroma, peritoneal macrophages, and white blood cells that aid tumor growth inhibition • Downregulates VEGFR in tumor, and vascular sprouting 	(Cho et al. 2005; Mayorek et al. 2010; Rana et al. 2015; Al-Nimer et al. 2015; Pantziarka et al. 2016)

synthase (PGHS) enzymes and hence have the ability to inhibit tumorigenesis (Zappavigna et al. 2020). In 1971, Vane was the first to establish a relationship between the mechanism of inhibition of COX activity by aspirin and NSAIDs (Vane 1971). Research data suggest that NSAIDs may prove effective chemoprophylaxis agents in patients with hereditary colorectal cancer syndromes and sporadic colorectal Cancer (Sangha et al. 2005). In colorectal cancer, the COX-2/PGE2 signaling pathway has been played a vital role (Roberts et al. 2011).

Similarly, Lichtenberger and his team in colorectal cancer showed that modified NSAIDs Aspirin and Indomethacin with phosphatidylcholine showed higher efficacy when used in combination. The use of phosphatidylcholine modifies these drugs gastrointestinal (GI) -safer NSAIDs (Lichtenberger et al. 2018). In 2020, Cairat and co-workers reported the use of aspirin or any other selective COX-2 inhibitors along with proton pump inhibitor (PPI) in reducing breast cancer risk in postmenopausal women (Cairat et al. 2020). Few inflammation targets have been studied in combating inflammation linked with cancer are COX, NF- κ B, cytokines/chemokines and their receptors, FGF and its receptor, and VEGF. These targets are seen overexpressed in many cancers, including breast, colorectal, lung, prostate, head and neck, cervical cancer. The study by Leahy and et al. mentioned overexpressed COX-2, an isoform of COX linked with angiogenesis, and the use of the drug celecoxib to block COX-2 reduces angiogenesis, hence proliferation and invasion (Leahy et al. 2002). NSAIDs drugs and their effects have been summarized in Table 5. Kostadinov et al. suggest that aspirin slows down somatic evolution by lowering DNA mutation accumulation, thus preventing esophageal adenocarcinoma (Kostadinov et al. 2013). Liu et al. summarized results from meta-analysis, where they have found no significant link between the use of aspirin and other NSAIDs with brain cancer (Liu et al. 2014). In contrast, new breakthrough studies result found that liquid aspirin can cross the blood-brain barrier (BBB) and destroy brain cancer cells with ten-fold higher efficacy compared with other chemotherapy drugs (unable to cross BBB).

Also, some NSAIDs enhance chemotherapeutics' sensitivity to tumors. For example, indomethacin (NSAIDs drug) produces a synergetic efficacy effect in combination with Adriamycin and cisplatin in glioblastoma and colorectal cancer (Hattori et al. 2001). Recently, a combination of aspirin and clopidogrel (antiplatelet drugs) enhanced immunotherapy (adoptive T cell therapy) for melanoma treatment (Rachidi et al. 2017). Moreover, existing literature recommends that NSAIDs prevents cancer from escaping immune surveillance. Data supported this that aspirin being a COX inhibitor inhibits the synthesis of PGE2 (increase amount of PGE2 aids cancer cells to hid by attenuating the immune system), which results in rejuvenation (re-activation) immune system (Wong 2019).

Hence, the application of NSAIDs has been a boom in the prevention and treatment of cancer. Recent studies also showed that early use of NSAIDs obstruct and inhibit the SARS CoV-2 produced inflammation produced by SARS CoV-2, resulting in the prevention of COVID-19 complications. In contrast, early use of glucocorticoids (steroids) might encourage the development of COVID-19 complications (Kelleni 2021).

Conclusion and future perspectives

A plethora of environmental mutagens, including physical, chemical, radiations, infectious agents, and endogenous agents such as hypoxia, free radicals, etc., are capable of inducing DNA lesions in the genome, which results in DNA damage followed by mutation and consequentially lead to carcinogenesis. Even though cells have evolved repair systems and cell cycle checkpoints to combat the detrimental outcomes of chemical modifications, chromosomal breakage, and genome instability to restore to a normal state. However, genetic and epigenetic changes affect many physiological processes because of dysfunctional DNA repair mechanisms and checkpoints' failure (including cell cycle checkpoints and immune checkpoints).

At present, only mutator genes have been recognized on the basis of the role they have in human diseases that are inherited. As numeral genes are involved in the replication, recombination, and repair process, and thus in the future, it is likely that many more such genes will be discovered, and that can further provide some future directives in the pathogenesis of specific cancers. Also, many new treatment modalities at present aim at sequencing the DNA which can serve to act as an influential tool. Moreover, a promising new time of malignancy therapeutics with specialists that repress explicit development stimulatory pathways is tracking down another specialty in our armamentarium in the conflict against disease. Designated malignancy therapeutics, like cytotoxic chemotherapies, refined monoclonal antibodies (mAbs), and tyrosine kinase inhibitors (TKIs), are among the significant therapy choices for the disease today as well as future. Designated treatments are more specific for malignancy cells and work on the personal satisfaction of disease patients going through treatment. A considerable lot of these medications have been supported by the FDA, and a few more are being concentrated in clinical preliminaries. In spite of the fact that the advancement of designated therapeutics has further developed malignant growth therapy altogether, the brutal truth is that the "Battle on Cancer" actually exists. Significant difficulties actually exist with the presently advertised inhibitors, incorporating constraints related to mAbs and TKIs drug types, gained instruments of medication obstruction that cause patient to backslide, and cancer heterogeneity. Today, there is a

dire requirement for the advancement of the novel enemies of growth specialists that are less expensive, stable, can specifically target disease subordinate pathways without influencing ordinary cells, and in particular, stay away from the improvement of opposition instruments. Peptide impersonates have the likely advantages of being exceptionally specific, steady, modest, and non-harmful. The focal point of this audit is to talk about the drawbacks related to the utilization of monoclonal antibodies and tyrosine kinase inhibitors. An exceptional accentuation will be set on endeavors taken in our research facility to (1) plan peptide antibodies and therapeutics that target subordinate disease pathways and (2) utilize a blended approach that will close down elective instruments that lead to obstruction.

Herein, we have summarized the various sources and types of DNA damage caused by different mutagenic agents that are carcinogenic in nature and how they lead to DNA replication errors, DNA adduct formations, oxidative stress, inflammation, as well as the failure of immune surveillance. All these eventually contribute and result in a different type of cancer. Moreover, we have also explained the genetic and epigenetic effects caused due to damaged DNA and its association with immunotherapy. Using these damaged DNA biomarkers as a tool for diagnosis and prognosis would greatly facilitate and enhance our capacity to identify the most crucial risk factors causing cancer. Indeed, to facilitate the development of new and contemporary preventive and therapeutic approaches, future more in-depth research is still necessary continue in order to enhance our understanding and compact cancer. Advance studies are needed to fully elucidate which lesions or cell types are more responsive to cancer prevention or treatment with anti-inflammatory agents, anti-viral therapies, and other chemotherapies. Also, additional focus is required to expand the horizon of Therapeutics Avenue including immune therapies, viral-related therapies, NSAIDs drugs, and other chemotherapeutic drugs and inhibitors.

Abbreviations AST, advanced solid tumor; ATR, ATR serine/threonine kinase; CRPC, castrate-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DDR, DNA damage repair; ICI, immunecheckpoint inhibitor; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PARP, poly [ADP-ribose] polymerase 1; PD-1, programmed cell death-1; TNBC, triple-negative breast cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein-Barr virus; HPV, human papillomavirus; HTLV-1, human T cell lymphotropic virus type 1; KSHV, Kaposi's associated sarcoma virus; MCV, Merkel cell polyomavirus; HHV4, human herpesvirus 4; HHV8, human herpesvirus 8; SV 40, simian virus 40; HCC, hepatocellular carcinoma; AIDS-KS, AIDS-Kaposi's sarcoma; ATL, adult T cell lymphoma; PTL, post-transplant lymphoproliferative disorder; NPC, nasopharyngeal carcinoma; HL, Hodgkin's lymphoma; MCC, Merkel cell carcinoma; NHL, non-Hodgkin lymphoma; GBM, glioblastoma multiforme; CRC, colorectal cancer; HAART, highly active antiretroviral therapy; PI-based HAART, protease inhibitor (PI)-based HAART; NNRTI, non-nucleoside

reverse transcriptase inhibitor; PGs, prostaglandins; CKGPEC, chitosan-Kheri gum polyelectrolyte complex; ATM, ataxia telangiectasia mutated; ATR, Ataxia telangiectasia and RAD3-related; HMGB1, high mobility group box 1; MITC, 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide

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