Chapter 16

DNA Damage, DNA Repair and Cancer

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Additional information is available at the end of the chapter

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1. Introduction

DNA damage appears to be a fundamental problem for life. In this chapter we review evidence indicating that DNA damages are a major primary cause of cancer. DNA damages give rise to mutations and epimutations that, by a process of natural selection, can cause progression to cancer. First, we describe the distinguishing characteristics of DNA damage, mutation and epimutation.

DNA damage is a change in the basic structure of DNA that is not itself replicated when the DNA is replicated. A DNA damage can be a chemical addition or disruption to a base of DNA (creating an abnormal nucleotide or nucleotide fragment) or a break in one or both chains of the DNA strands. When DNA carrying a damaged base is replicated, an incorrect base can often be inserted opposite the site of the damaged base in the complementary strand, and this can become a mutation in the next round of replication. Also DNA double-strand breaks may be repaired by an inaccurate repair process leading to mutations. In addition, a double strand break can cause rearrangements of the chromosome structure (possibly disrupting a gene, or causing a gene to come under abnormal regulatory control), and, if such a change can be passed to successive cell generations, it is also a form of mutation. Mutations, however, can be avoided if accurate DNA repair systems recognize DNA damages as abnormal structures, and repair the damages prior to replication. As illustrated in Figure 1, when DNA damages occur, DNA repair is a crucial protective process blocking entry of cells into carcinogenesis.

We note that DNA damages occur in both replicating, proliferative cells (e.g. those forming the internal lining of the colon or blood forming "hematopoietic" cells), and in differentiated, non-dividing cells (e.g. neurons in the brain or myocytes in muscle). Cancers occur primarily in proliferative tissues. If DNA damages in proliferating cells are not repaired due to

inadequate expression of a DNA repair gene, this increases the risk of cancer. In contrast, when DNA damages occur in non-proliferating cells and are not repaired due to inadequate expression of a DNA repair gene, the damages can accumulate and cause premature aging. As examples, deficiencies in DNA repair genes *ERCC1* or *XPF* [1] or in *WRN* [2, 3] cause both increased risk of cancer as well as premature aging. In Figure 1, DNA repair is indicated as a crucial process impeding both cancer and premature aging.

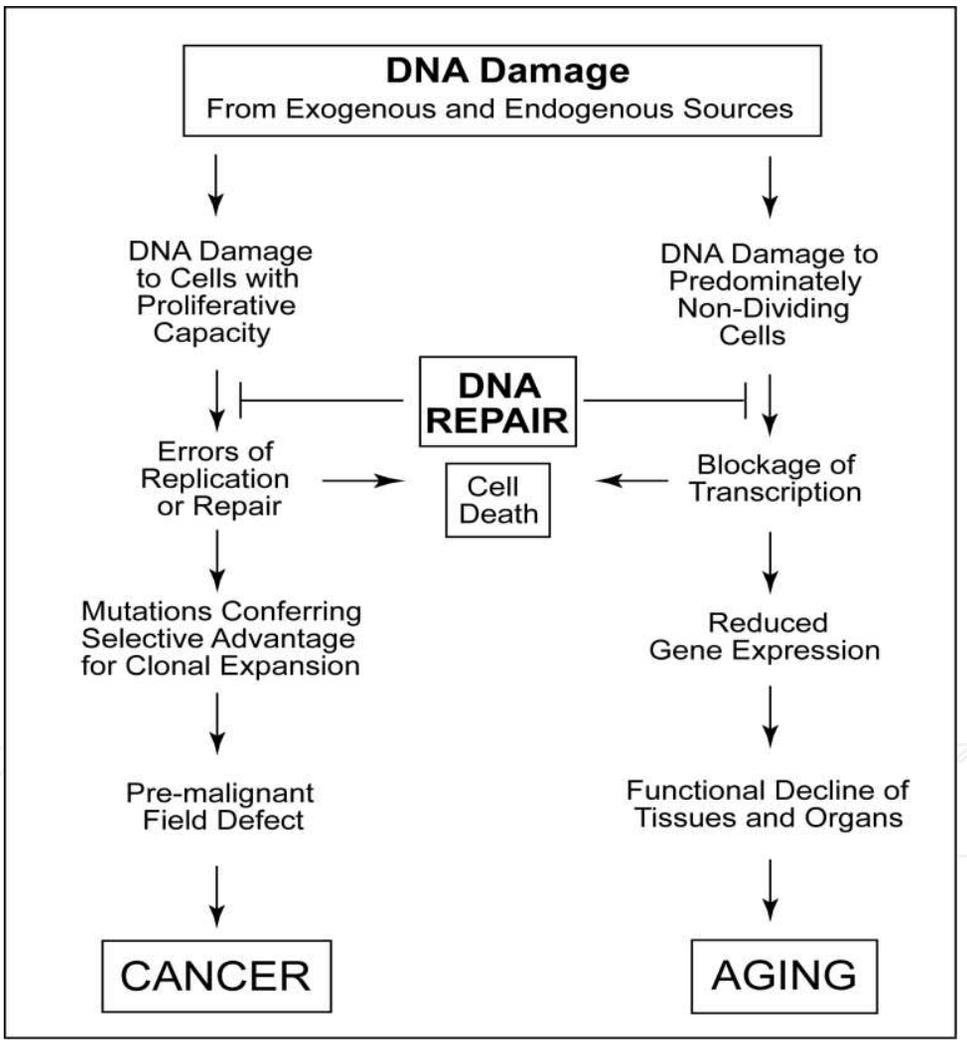

Figure 1. The roles of DNA damage and DNA repair in cancer and aging.

A mutation is a change in the DNA sequence in which normal base pairs are substituted, added, deleted or rearranged. The DNA containing a mutation still consists of a sequence of standard base pairs, and the altered DNA sequence can be copied when the DNA is replicated. A mutation can prevent a gene from carrying out its function, or it can cause a gene to be translated into a protein that functions abnormally. Mutations can activate oncogenes, inactivate tumor suppressor genes or cause genomic instability in replicating cells, and an assemblage of such mutations, together in the same cell, can lead to cancer. Cancers usually arise from an assemblage of mutations conferring a selective advantage that leads to clonal expansion (Figure 1). Colon cancers, for example, have an average of 15 "driver" mutations (mutations occurring repeatedly in different colon cancers) and about 75 "passenger" mutations (mutations occurring infrequently in colon cancers) [4, 5]. Colon cancers also were found to have an average of 9 duplications or deletions of chromosome segments [6] or, more recently, 17 focal amplifications, 28 recurrent deletions and up to 10 translocations [5]. Since mutations have normal DNA structure, they cannot be recognized or removed by DNA repair processes in living cells. Removal of a mutation only occurs if it is sufficiently deleterious to cause the death of the cell.

Another type of inheritable alteration, similar in some ways to a mutation, is an epigenetic change. An epigenetic change refers to a functionally relevant modification of the DNA, or of the histone proteins controlling the relaxation or tightened winding of the DNA within their nucleosome structures. Some epigenetic changes involve specific alterations of the DNA nucleotides. Examples of such changes include methylation of the DNA at particular sites (CpG islands) where the DNA starts to be transcribed into RNA. These changes may inhibit transcription. Other epigenetic changes involve modification of histones associated with particular regions of the DNA. These may inhibit or promote the ability of these regions to be transcribed into mRNA. Methylation of CpG islands or modification of histones can directly alter transcription of gene-encoded mRNAs but they can also occur in parts of the genome that code for microRNAs (miRNAs). MiRNAs are endogenous short non-protein coding RNAs (~22 nucleotides long) that post-transcriptionally regulate mRNA expression in a sequence specific manner. miRNAs either cause degradation of mRNAs or block their translation. Epigenetic modifications can play a role similar to mutation in carcinogenesis, and about 280 cancer prone epigenetic alterations are listed by Schnekenburger and Diederich [7]. Epigenetic alterations are usually copied onto the daughter chromosomes when the parental chromosome replicates.

Although epigenetic changes can be passed down from one cell generation to the next, they are not regarded as true mutations. Most epigenetic changes appear to be part of the differentiation program of the cell and are necessary to allow different types of cells to carry out different functions. In most cells of a human body, only about 5% of genes are active at any one time, often due to epigenetic modifications. However, abnormal unprogrammed epigenetic changes may also occur that alter the functioning of a cell and these changes are referred to as "epimutations." Programmed epigenetic changes can be reversed. During development, as daughter cells of a stem cell differentiate, some epige-

netic changes are programmed for reversal. However, a double strand break in DNA (a type of DNA damage) can initiate unprogrammed epigenetic gene silencing both by causing methylation of a CpG island as well as by promoting silencing types of histone modifications [8]. Another form of epigenetic silencing may occur during DNA repair. The enzyme Parp1 (poly(ADP)-ribose polymerase) and its product poly(ADP)-ribose (PAR) accumulate at sites of DNA damage as part of a repair process [9]. This, in turn, directs recruitment and activation of the chromatin remodeling protein ALC1 that may cause nucleosome remodeling [10]. Nucleosome remodeling has been found to cause, for instance, epigenetic silencing of DNA repair gene *MLH1* [11]. Chemicals previously identified as DNA damaging agents, including benzene, hydroquinone, styrene, carbon tetrachloride and trichloroethylene, were shown to cause considerable hypomethylation of DNA, some through the activation of oxidative stress pathways [12]. Dietary agents also have been shown to affect DNA methylation or histone modification by numerous pathways [13]. Recent evidence indicates that epimutations occur in DNA repair genes that reduce their function. Epimutations in DNA repair genes allow DNA damages to accumulate, and are a cause of progression to cancer [14].

2. DNA damages are frequent, and DNA repair processes can be overwhelmed

Tens of thousands of DNA damages occur per day per cell, on average, in humans, due to reactive molecules produced by metabolism or by hydrolytic reactions in the warm aqueous cellular media. Some types of such endogenous damages, and their rates of occurrence, are shown in Table 1.

A considerable number of other types of endogenous DNA damages have been identified, many of which are mutagenic. These include propano-, etheno- and malondialdehyde-derived DNA adducts, base propenals, estrogen-DNA adducts, alkylated bases, deamination of each of cytosine, adenine and guanine (to form uracil, hypoxanthine and xanthine, respectively) and adducts formed with DNA by reactive carbonyl species [15].

While there are repair pathways that act on these DNA damages, the repair processes are not 100% efficient, and further damages occur even as current DNA damages are being repaired. Thus there is a steady state level of many DNA damages, reflecting the efficiencies of repair and the frequencies of occurrence. For instance, Helbock et al. [16] estimated the steady state level of oxidative adducts in rat liver as 24, 000 adducts per cell in young rats and 66, 000 adducts per cell in old rats. Nakamura and Swenberg [17] determined the number of AP sites (apurinc and apyrimidinic sites) in normal tissues of the rat (i.e. in lung, kidney, liver, testis, heart, colon and brain). The data indicated that the number of AP sites ranged from about 50, 000 per cell in liver, kidney and lung to about 200, 000 per cell in the brain. These steady state numbers of AP sites in genomic DNA were considered to represent the balance between formation and repair of AP sites.

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DNA damages	Reported rate of occurrence	Ref.
Oxidative	86,000 per cell per day in rats	[18]
	10,000 per cell per day in humans 100,000 per cell per day in rats	[19]
	11,500 per cell per day for humans 74,000 per cell per day for rats	[16]
Specific oxidative damage products 8-hydroxyguanine, 8-hydroxydeoxyguanosine, 5-(hydroxymethyl) uracil	2,800 per cell per day in humans 34,800 per cell per day in mice	[20]
Depurinations	10,000 per cell during 20-hour generation period	[21]
	13,920 per cell per day (580/cell/hr)	[22]
	2,000 to 10,000 per cell per day	[23,24]
	9,000 per cell per day	[25]
Depyrimidinations	500 pyrimidines per cell during 20-hour generation period	[21]
	696 per cell per day (29/cell/hr)	[22]
Single-strand breaks	55,200 per cell per day (2,300/cell/hr)	[22]
Double-strand breaks	~10 per cell cycle in humans	[26]
	~50 per cell cycle in humans	[27]
O^6-methylguanine	3,120 per cell per day (130/cell/hr)	[22]
Cytosine deamination	192 per cell per day (8/cell/hr)	[22]

Table 1. DNA damages due to natural endogenous causes in mammalian cells

DNA repair pathways are usually able to keep up with the endogenous damages in replicating cells, in part by halting DNA replication at the site of damage until repair can occur [28, 29]. In contrast, non-replicating cells have a build-up of DNA damages, causing aging [30, 31].

However, some exogenous DNA damaging agents, such as those in tobacco smoke, discussed below, may overload the repair pathways, either with higher levels of the same type of DNA damages as those occurring endogenously or with novel types of damage that are repaired more slowly. In addition, if DNA repair pathways are deficient, due to inherited mutations or sporadic somatic epimutations in DNA repair genes in replicating somatic cells, unrepaired endogenous and exogenous damages will increase due to insufficient repair. Increased DNA damages would likely give rise to increased errors of replication past the damages (by trans-lesion synthesis) or increased error prone repair (e.g. by non-homologous end-joining), causing mutations. Increased mutations that activate oncogenes, inactivate tumor suppressor genes, cause genomic instability or give rise to other driver mutations in replicating cells would increase the risk of cancer.

3. Cancers are often caused by exogenous DNA damaging agents

Cancer incidence, in different areas of the world, varies considerably. Thus, the incidence of colon cancer among Black Native-Africans is less than 1 person out of 100, 000, while among male Black African-Americans it is 72.9 per 100, 000, and this difference is likely due to differences in diet [32, 33]. Rates of colon cancer incidence among populations migrating from lower-incidence to higher-incidence countries change rapidly, and within one generation can reach the rate in the higher-incidence country. This is observed, for instance, in migrants from Japan to Hawaii [34].

The most common cancers for men and women and their rates of incidence per 100, 000, averaged over the more developed areas and less developed areas of the world, are shown in Table 2 (from [35]). Overall, worldwide, cancer incidence in all organs combined is 300.1 per 100, 000 per year in more developed areas and 160.3 per 100, 000 per year in less developed areas [35]. The differences in cancer incidence between more developed areas of the world and less developed areas are likely due, in large part, to differences in exposure to exogenous carcinogenic factors. The lowest rates of cancers in a given organ (Table 2) may be due, at least in part, to endogenous DNA damages (as described in the previous section) that cause errors of replication (trans-lesion synthesis) or error prone repair (e.g. non-homologous end-joining), leading to carcinogenic mutations. The higher rates (Table 2) are likely largely attributable to exogenous factors, such as higher rates of tobacco use or diets higher in saturated fats that directly, or indirectly, increase the incidence of DNA damage.

It is interesting to note in Table 2 that, in cases where cancers occur in the same organs of men and women, men consistently have a higher rate of cancer than women. The basis for this is currently unknown.

	More developed areas		Less developed areas	
	Incidence	***Mortality***	***Incidence***	***Mortality***
Breast (women)	66.4	15.3	27.3	10.8
Prostate (men)	62.0	10.6	12.0	5.6
Lung (men)	47.4	39.4	27.8	24.6
Lung (women)	18.6	13.6	11.1	9.7
Colorectum (men)	37.6	15.1	12.1	6.9
Colorectum (women)	24.2	9.7	9.4	5.4
Esophagus (men)	6.5	5.3	11.8	10.1
Esophagus (women)	1.2	1.0	5.7	4.7
Stomach (men)	16.7	10.4	21.1	16.0
Stomach (women)	7.3	4.7	10.0	8.1
Liver (men)	8.1	7.2	18.9	17.4
Liver (women)	2.7	2.5	7.6	7.2
Bladder (men)	16.6	4.6	5.4	2.6
Bladder (women)	3.6	1.0	1.4	0.7
Cervix/Uterine (women)	12.9	2.4	5.9	1.7
Kidney (men)	11.8	4.1	2.5	1.3
Kidney (women)	5.8	1.7	1.4	0.8
Non-Hodgkin lymphoma (men)	10.3	3.6	4.2	3.0
Non-Hodgkin lymphoma (women)	7.0	2.2	2.8	1.9
Melanoma (men)	9.5	1.8	0.7	0.3
Melanoma (women)	8.6	1.1	0.6	0.3
Ovarian (women)	9.4	5.1	5.0	3.1

Table 2. Incidence and mortality rates for the most common cancers in age standardized rates per 100, 000 (excluding non-melanoma skin cancer) (Adapted from Jemal et al. [35]).

4. Exogenous DNA damaging agents in carcinogenesis

Carcinogenic exogenous factors have been identified as a major cause of many common cancers, including cancers of the lung, colorectum, esophagus, stomach, liver, cervix/uterus and melanoma. Often such exogenous factors have been shown to cause DNA damage, as described below.

5. Exogenous DNA damaging agents in lung cancer

In both developed and undeveloped countries, lung cancer is the most frequent cause of cancer mortality (Table 2, data for men and women combined). Lung cancer is largely caused by tobacco smoke, since risk estimates for lung cancer indicate that, in the United States, tobacco smoke is responsible for 90% of lung cancers. Also implicated in lung cancer (and somewhat overlapping with smoking) are occupational exposure to carcinogens (approximately 9 to 15%), radon (10%) and outdoor air pollution (perhaps 1 to 2%) [36].

Acrolein	122.4
Formaldehyde	60.5
Acrylonitrile	29.3
1,3-butadiene	105.0
Acetaldehyde	1448.0
Ethylene oxide	7.0
Isoprene	952.0
Benzo[a]pyrene	0.014

Table 3. Weight, in μg per cigarette, of several likely carcinogenic DNA damaging agents in tobacco smoke (from [37] Cunningham et al., 2011])

Tobacco smoke is a complex mixture of over 5, 300 identified chemicals, of which 150 are known to have specific toxicological properties (see partial summary by Cunningham [37]). A "Margin of Exposure" approach has recently been established to determine the most important exogenous carcinogenic factors in tobacco smoke [37]. This quantitative-type of measurement is based on published dose response data for mutagenicity or carcinogenicity and the concentrations of these components in tobacco smoke (Table 3). Using the "Margin of Exposure" approach, Cunningham et al. [37] found the most important tumorigenic compounds in tobacco smoke to be, in order of importance, acrolein, formaldehyde, acrylonitrile, 1, 3-butadiene, acetaldehyde, ethylene oxide and isoprene.

Acrolein, the first agent in Table 3, is the structurally simplest α, β-unsaturated aldehyde (Figure 2). It can rapidly penetrate through the cell membrane and bind to the nucleophilic N^2-amine of deoxyguanine (dG) followed by cyclization of N1, to give the exocyclic DNA adduct α-hydroxy-1, N^2-propano-2′-deoxyguanine (α-HOPdG) (shown in Figure 2) and another product designated γ-HOPdG. The adducts formed by acrolein are a major type of DNA damage caused by tobacco smoke, and acrolein has been found to be mutagenic [38].

In tobacco smoke, acrolein has a concentration >8, 000 fold higher than benzo[a]pyrene (reviewed in [38]), with 122.4 μg of acrolein per cigarette. Benzo[a]pyrene has long been thought to be an important carcinogen in tobacco smoke [39]. As reviewed by Alexandrov et

al. [39], benzo[a]pyrene damages DNA by forming DNA adducts at the N^2 position of guanine (similar to where acrolein forms adducts). However, by the "Margin of Exposure" approach, based on published dose response data and its concentration in cigarette smoke of 0.014 μg per cigarette, benzo[a]pyrene is thought to be a much less important mutagen for lung tissue than acrolein and the other six highly likely carcinogens in tobacco smoke listed in Table 3 [37].

The other agents in Table 3 cause DNA damages in different ways. Formaldehyde, the second agent in Table 3, primarily causes DNA damage by introducing DNA-protein cross-links. These cross-links, in turn, cause mutagenic deletions or other small-scale chromosomal rearrangements [40] and may also cause mutations through single-nucleotide insertions [41]. Acrylonitrile, the third agent in Table 3, appears to cause DNA damage indirectly by increasing oxidative stress, leading to increased levels of 8'-hydroxyl-2-deoxyguanosine (8-OHdG) in DNA [42]. Oxidative stress also causes lipid peroxidation that generates malondialdehyde (MDA), and MDA forms DNA adducts with guanine, adenine and cytosine [43]. The fourth agent in Table 3, 1, 3-butadiene, causes genotoxicity both directly by forming a DNA adduct as well as indirectly by causing global loss of DNA methylation and histone methylation leading to epigenetic alterations [44]. The fifth agent in Table 3, acetaldehyde, reacts with 2'-deoxyguanosine in DNA to form DNA adducts [45]. The sixth agent in Table 3, ethylene oxide, forms mutagenic hydroxyethyl DNA adducts with adenine and guanine [46]. The seventh agent in Table 3, isoprene, is normally produced endogenously by humans, and is the main hydrocarbon of non-smoking human breath [47]. However, smoking one cigarette causes an increase of breath isoprene levels by an average of 70% [48]. Isoprene, after being metabolized to mono-epoxides, causes DNA damage measured as single and double strand breaks in DNA [49].

A large number of studies have been published in which the levels and characteristics of DNA adducts in the lung and bronchus of smokers and non-smokers have been compared, as reviewed by Phillips [50]. In most of these studies, significantly elevated levels of DNA adducts were detected in the peripheral lung, bronchial epithelium or bronchioalveolar lavage cells of the smokers, especially for total bulky DNA adducts. As further discussed by Phillips [50], mean levels of DNA adducts in ex-smokers (usually with at least a 1 year interval since smoking cessation) are found generally to be intermediate between the levels of smokers and life-long non-smokers. From these comparisons, the half-life of some DNA adducts in lung tissue are estimated to be ~1–2 years.

6. Exogenous DNA damaging agents in colorectal cancer

Up to 20% of current colorectal cancers in the United States may be due to tobacco smoke [51]. Presumably tobacco smoke causes colon cancer due to the DNA damaging agents described above for lung cancer. These agents may be taken up in the blood and carried to organs of the body.

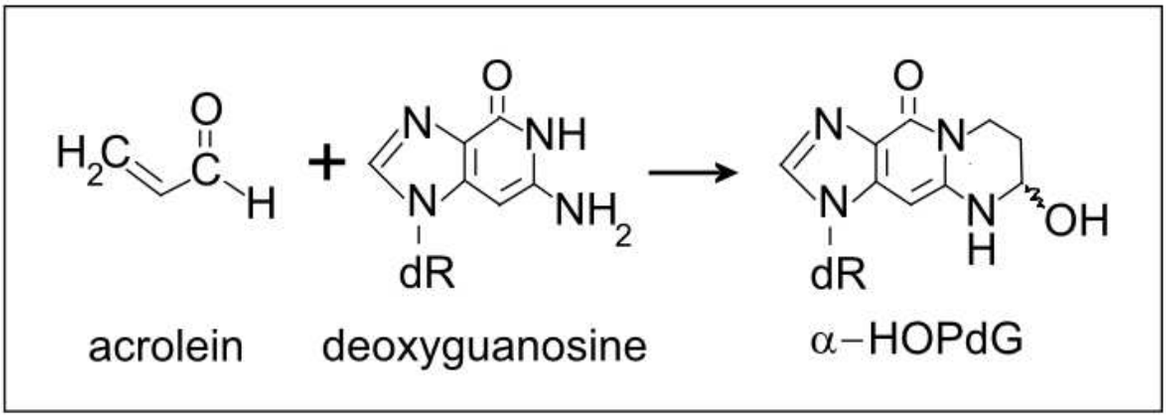

Figure 2. Reaction of acrolein with deoxyguanosine

The human colon is exposed to many compounds that are either of direct dietary origin or result from digestive and/or microbial processes. Four different classes of colonic mutagenic compounds were analysed by de Kok and van Maanen [52] and evaluated for fecal mutagenicity. These included (1) pyrolysis compounds from food (heterocyclic aromatic amines and polycyclic aromatic hydrocarbons), (2) *N*-nitroso-compounds (from high meat diets, from drinking water with high nitrates or produced during ulcerative colitis), (3) fecapentaenes (produced by the colonic bacteria *Bacteriodes* in the presence of bile acids) and (4) bile acids (increased in the colon in response to a high fat diet and metabolized to genotoxic form by bacteria in the colon). Many of these diet-related mutagenic compounds were analysed by Pearson et al. [53] in terms of their presence in fecal water, and their effect on the cytotoxic or genotoxic activity of fecal water. Evidence in both of these studies was insufficient to evaluate the colorectal cancer risk as a result of specific exposures in quantitative terms.

However, substantial evidence implicates bile acids (the 4th possibility above) in colon caner. Bernstein et al. [54], summarized 12 studies indicating that the bile acids deoxycholic acid (DCA) and/or lithocholic acid (LCA) induce production of DNA damaging reactive oxygen species and/or reactive nitrogen species in colon cells of animal or human origin. They also tabulated 14 studies showing that DCA and LCA induce DNA damage in colon cells. In addition to causing DNA damage, bile acids may also generate genomic instability by causing

mitotic perturbations and reduced expression of spindle checkpoint proteins, giving rise to micro-nuclei, chromosome bridges and other structures that are precursors to aneuploidy [55]. Furthermore, at high physiological concentrations, bile acids cause frequent apoptosis, and those cells in the exposed populations with reduced apoptosis capability tend to survive and selectively proliferate [54, 56]. Cells with reduced ability to undergo apoptosis in response to DNA damage would tend to accumulate mutations when replication occurs past those damages, and such cells may give rise to colon cancers. In addition, 7 epidemiological studies between 1971 and 1990 (reviewed by Bernstein et al. [54]), found that fecal bile acid concentrations are increased in populations with a high incidence of colorectal cancer. A similar 2012 epidemiological study showed that concentrations of fecal LCA and DCA, respectively, were 4-fold and 5-fold higher in a population at 65-fold higher risk of colon cancer compared to a population at lower risk of colon cancer [32]. This evidence points to bile acids DCA and LCA as centrally important DNA-damaging carcinogens in colon cancer.

Dietary total fat intake and dietary saturated fat intake is significantly related to incidence of colon cancer [57]. Increasing total fat or saturated fat in human diets results in increases in DCA and LCA in the feces [58, 59], indicating increased contact of the colonic epithelium with DCA and LCA. Bernstein et al. [60] added the bile acid DCA to the standard diet of wild-type mice. This supplement raised the level of DCA in the feces of mice from the standard-diet fed mouse level of 0.3 mg DCA/g dry weight to 4.6 mg DCA/g dry weight, a level similar to that for humans on a high fat diet of 6.4 mg DCA/g dry weight. After 8 or 10 months on the DCA-supplemented diet, 56% of the mice developed invasive colon cancer. This directly indicates that DCA, a DNA damaging agent, at levels present in humans after a high fat diet, can cause colorectal cancer.

7. Exogenous DNA damaging agents implicated in other major cancers

It is beyond the scope of this chapter to detail the evidence implicating DNA damaging agents as etiologic agents in all of the significant cancers. Therefore, in Table 4 we indicate with a single reference the major DNA damaging agent in five additional prevalent cancers, in order to illustrate the generality of exogenous DNA damaging agents as causes of cancer. In particular, we point out, as reviewed by Handa et al. [61], *Helicobacter pylori* infection increases the production of reactive oxygen and reactive nitrogen species (RNS) in the human stomach, which, in turn, significantly increases DNA damage in the gastric epithelial cells. Thus, *H. pylori* infection acts as a DNA damaging agent. In the case of human papillomavirus (HPV) infection, Wei et al. [62] showed that cervical cells could resist RNS stress when not infected with HPV. However, cervical cells infected by HPV and exposed to RNS had higher levels of DNA double strand breaks as well as a higher mutation rate. This appeared to occur due to the ability of HPV to greatly reduce protein expression of the DNA damage repair/response gene *P53* when infected cells were stressed by RNS. Since reduced *P53* expression leads to greater RNS-induced DNA damage, HPV infection acts as a DNA damaging agent in the presence of RNS stress.

Cancer	Exogenous DNA damaging agent	Ref.
Esophagus	Bile acids	[63]
Stomach	*Helicobacter pylori* infection	[61]
Liver	*Aspergillus* metabolite aflatoxin B(1)	[64]
Cervix/Uterus	Human papillomavirus plus increased nitric oxide from tobacco smoke or other infection	[62]
Melanoma	UV light from solar radiation	[65]

Table 4. Selected cancers and relevant implicated exogenous DNA damaging agents

8. Deficient DNA repair due to a germ line mutation allows DNA damages to increase, leading to increased frequencies of mutation, epimutation and cancer

Expression of DNA repair genes may be reduced by inherited germ line mutations or genetic polymorphisms, or by epigenetic alterations or mutations in somatic cells, and these reductions may substantially increase the risk of cancer. Overall, about 30% of cancers are considered to be familial (largely due to inherited germ line mutations or genetic polymorphisms) and 70% are considered to be sporadic [66].

In 2 overlapping databases [67, 68] 167 and169 human genes (depending on the database) are listed that are directly employed in DNA repair or influence DNA repair processes. The lists were originally devised by Wood et al. [69, 70]. The genes are distributed in groups of DNA repair pathways and in related functions that affect DNA repair (Table 5). Bernstein et al. [71] illustrate many of the steps and order of action of the gene products involved for the first five DNA repair pathways listed in Table 5.

Individuals with an inherited impairment in DNA repair capability are often at considerably increased risk of cancer. If an individual has a germ line mutation in a DNA repair gene or a DNA damage response gene (that recognizes DNA damage and activates DNA repair), usually one abnormal copy of the gene is inherited from one of the parents and then the other copy is inactivated at some later point in life in a somatic cell. The inactivation may be due, for example, to point mutation, deletion, gene conversion, epigenetic silencing or other mechanisms [72]. The protein encoded by the gene will either not be expressed or be expressed in a mutated form. Consequently the DNA repair or DNA damage response function will be deficient or impaired, and damages will accumulate. Such DNA damages can cause errors during DNA replication or inaccurate repair, leading to mutations that can give rise to cancer.

Increased oxidative DNA damages also cause increased gene silencing by CpG island hypermethylation, a form of epimutation. These oxidative DNA damages induce formation and relocalization of a silencing complex that may result in cancer-specific aberrant DNA

methylation and transcriptional silencing [73]. As pointed out above, the enzyme Parp1 (poly(ADP)-ribose polymerase) and its product poly(ADP)-ribose (PAR) accumulate at sites of DNA damage as part of a repair process [9], recruiting chromatin remodeling protein ALC1, causing nucleosome remodeling [10] that has been shown to direct epigenetic silencing of DNA repair gene *MLH1* [11]. If silencing of genes necessary for DNA repair occurs, the repair of further DNA damages will be deficient and more damages will accumulate. Such additional DNA damages will cause increased errors during DNA synthesis, leading to mutations that can give rise to cancer.

	Number of genes listed in the two databases
Homologous Recombinational Repair (HRR)	21,21
Non-homologous End Joining (NHEJ)	8,7
Nucleotide Excision Repair (NER)	30,29
Base Excision Repair (including PARP enzymes) (BER)	19,20
Mis-Match Repair (MMR)	11,10
Fanconi Anemia (FANC) [affects HRR (above) and translesion synthesis (TLS)]	10,16
Direct reversal of damage	3,3
DNA polymerases (act in various pathways)	17,15
Editing and processing nucleases (act in various pathways)	6,8
Ubiquitination and modification/Rad6 pathway including TLS	11,5
DNA damage response	12,14
Modulation of nucleotide pools	3,3
Chromatin structure	2,3
Defective in diseases and syndromes	4,5
DNA-topoisomerase crosslinks	2,1
Other genes	8,9

Table 5. DNA repair pathways and other processes affecting DNA repair [67, 68]

9. Inherited mutations in genes employed in DNA repair that give rise to syndromes characterized by increased risk of cancer.

Table 6 lists 36 genes for which an inherited mutation results in an increased risk of cancer. The proteins encoded by 35 of these genes are involved in DNA repair and in some cases also in other aspects of the DNA damage response such as cell cycle arrest and apoptosis. The polymerase coded for by the 36th gene, *XPV (POLH)*, is involved in bypass (rather than repair) of DNA damage, called translesion synthesis. The genes listed in Table 6, when mutated in the germ line, give rise to a considerably increased lifetime risk of cancer, of up to 100% (e.g. p53 mutations [74]). Thus defects in DNA repair cause progression to cancer.

In addition to mutations in genes that may substantially raise lifetime cancer risk, there appear to be many weakly effective genetically inherited polymorphisms [single nucleotide polymophisms (SNPs) and copy number variants (CNVs)]. By the HapMap Project, more than 3 million SNPs have been found, and by Genome Wide Association studies (GWAs), about 30 SNPs were found to increase risk of cancers. However the added risk of cancer by these SNPs is usually small, i.e. less than a factor of 2 increase [75]. A large twin study [66], involving 44, 788 pairs of twins, evaluated the risk of the same cancer before the age of 75 for monozygotic twins (identical genomes with the same polymorphisms) and dizygotic twins (having a 50% chance of the same polymorphisms). If one twin had colorectal, breast or prostate cancer, the monozygotic twin had an 11 to 18 percent chance of developing the same cancer while the dizygotic twin had only a 3 to 9% risk. The differences in monozygotic and dizygotic rates of paired cancer were not significant for the other 24 types of cancer evaluated in this study. Polymorphisms of the DNA repair gene ERCC1 will be discussed below in relation to targeted chemotherapy.

10. Epimutations may repress DNA repair gene expression, allowing DNA damages to increase, leading to increased frequency of further epimutation, mutation and cancer

While germ line (familial) mutations in DNA repair genes cause a high risk of cancer, somatic mutations in DNA repair genes are rarely found in sporadic (non-familial) cancers [4]. Much more often, DNA repair genes are found to have epigenetic alterations in cancers.

One example of the epigenetic down-regulation of a DNA repair gene in cancers comes from studies of the MMR protein MLH1. Truninger et al. [76] assessed 1, 048 unselected consecutive colon cancers. Of these, 103 were deficient in protein expression of *MLH1*, with 68 of these cancers being sporadic (the remaining *MLH1* deficient cancers were due to germ line mutations). Of the 68 sporadic MLH1 protein-deficient colon cancers, 65 (96%) were found to be deficient due to epigenetic methylation of the CpG island of the *MLH1* gene. Deficient protein expression of *MLH1* may also have been caused, in the remaining 3 sporadic MLH1 protein-deficient cancers (which did not have germ line mutations), by over expression of the microRNA miR-155. When miR-155 was transfected into cells it caused reduced expression of *MLH1* [77]. Overexpression of miR-155 was found in colon cancers in which protein expression of *MLH1* was deficient and the *MLH1* gene was neither mutated nor hypermethylated in its CpG island [77].

DNA repair gene(s)	Encoded protein	Repair pathway(s) affected	Ref.	Cancers with increased risk	Ref.
breast cancer 1 & 2	BRCA1, BRCA2	HRR of double strand breaks and daughter strand gaps	[85]	Breast, Ovarian	[86]
ataxia telangiectasia mutated	ATM	Different mutations in ATM reduce HRR, single strand annealing (SSA), NHEJ or homology directed double strand break rejoining (HDR)	[87]	Leukemia, Lymphoma, Breast	[87,88]
Nijmegen breakage syndrome	NBS	NHEJ	[89]	Lymphoid cancers	[89]
meiotic recombination 11	MRE11	HRR and NHEJ	[90]	Breast	[91]
Bloom's Syndrome (helicase)	BLM	HRR	[92]	Leukemia, Lymphoma, Colon, Breast, Skin, Auditory canal, Tongue, Esophagus, Stomach, Tonsil, Larynx, Lung, Uterus	[93]
Werner Syndrome (helicase)	WRN	HRR, NHEJ, long patch BER	[94]	Soft tissue sarcoma, Colorectal, Skin, Thyroid, Pancreatic	[95]
Rothman Thomson syndrome Rapadilino syndrome Baller Gerold syndrome	RECQ4	Helicase likely active in HRR	[96]	Basal cell carcinoma, Squamous cell carcinoma, Intraepidemial carcinoma	[97]
Fanconi's anemia gene FANC A,B,C,D1,D2,E,F,G,I,J,L,M,N	FANCA etc.	HRR and TLS	[98]	Leukemia, Liver tumors, Solid tumors many areas	[99]
xeroderma pigmentosa C, E [DNA damage binding protein 2 (DDB2)]	XPC XPE	Global genomic NER repairs damage in both transcribed and untranscribed DNA	[100, 101]	Skin cancer (melanoma and non-melanoma)	[100, 101]
xeroderma pigmentosa A, B, D, F, G	XPA XPB XPD XPF XPG	Transcription coupled NER repairs the transcribed strands of transcriptionally active genes	[102]	Skin cancer (melanoma and non-melanoma), Central nervous system cancers	[102]
xeroderma pigmentosa V (also called polymerase H)	XPV (POLH)	Translesion Synthesis (TLS)	[102]	Skin cancer (melanoma and non-melanoma)	[102]

DNA repair gene(s)	Encoded protein	Repair pathway(s) affected	Ref.	Cancers with increased risk	Ref.
mutS (E. coli) homolog 2 mutS (E. coli) homolog 6 mutL (E. coli) homolog 1 postmeiotic segregation increased 2 (S. cerevisiae)	MSH2 MSH6 MLH1 Pms2	MMR	[76]	Colorectal, endometrial. ovarian	[103]
mutY homolog (E. coli)	MUTYH	BER of A mispaired with 8OHdG, G, FapydG and C	[104]	Colon	[105]
ataxia telaniectsia and *RAD3* related	ATR	DNA damage response likely affects HRR, not NHEJ	[106]	Oropharyngeal cancer	[107]
Li Fraumeni syndrome	P53	HRR, BER, NER and DNA Damage Response for those and for NHEJ and MMR	[108]	Sarcoma, Breast, Lung, Skin, Pancreas, Leukemia, Brain	[74]

Table 6. Inherited mutations in DNA repair genes that increase the risk of cancer

Another example of the epigenetic down-regulation of a DNA repair gene in cancer comes from studies of the direct reversal of methylated guanine bases by methyl guanine methyl transferase (MGMT). In the most common form of brain cancer, glioblastoma, the DNA repair gene *MGMT* is epigenetically methylated in 29% [78] to 66% [79] of tumors, thereby reducing protein expression of MGMT. However, for 28% of glioblastomas, the MGMT protein is deficient but the *MGMT* promoter is not methylated [79]. Zhang et al. [78] found, in the glioblastomas without methylated *MGMT* promoters, that the level of microRNA miR-181d is inversely correlated with protein expression of MGMT and that the direct target of miR-181d is the MGMT mRNA 3′UTR (the three prime untranslated region of MGMT mRNA), though they indicated that other miRNAs may also be involved in the reduction of protein expression of MGMT.

Almost all DNA repair deficiencies found, so far, in sporadic cancers, and in precancerous tissues surrounding cancers (field defects) are due to epigenetic changes. Examples of such epigenetic alterations in DNA repair genes in different types of cancer are shown in Table 7. A recent review [80] lists 41 reports (mostly not overlapping with those listed in Table 7) indicating methylation of 20 DNA repair genes in various cancers. In Table 7 data are also shown on DNA repair gene deficiencies for the field defects associated with colorectal, gastric, laryngeal and non-small cell lung cancer.

As summarized above, epimutations can result from oxidative DNA damages. Such damages cause formation and relocalization of a silencing complex that in turn causes increased gene silencing by CpG island hypermethylation [73]. Epigenetic nucleosome remodeling during DNA repair can also silence gene expression [11]. When CpG island methylation or nucleosome remodeling or other types of epigenetic alterations (e.g. micro RNAs or histone modifications) inhibit DNA repair genes, more damages will accumulate. Accumulated DNA damages cause increased errors during DNA synthesis and repair. Thus epigenetic deficiencies in DNA repair genes can have a cascading effect (a mutator phenotype), leading to genomic instability and accumulation of mutations and epimutations that can give rise to cancer.

Cancer	Epigenetic changes in cancer (mechanism)	% sporadic cancers with epimutations	Epigenetic changes in field defect (mechanism)	% field defects with epi-mutations	Ref.
Breast	*BRCA1* (CGI*)	13% unselected 67% medullary 55% mucinous			[108]
	WRN (CGI)	17% unselected			[2]
Ovarian	*BRCA1* (CGI)	31% of those with loss of heterozygosity			[108]
Colorectal	*WRN* (CGI)	38%			[2]
	MGMT (CGI)	46%	*MGMT* (CGI)	23%	[109]
	MGMT (CGI)	90%			[110]
	MLH1 (CGI)	65%			
	MLH1 (CGI)	10%			[76]
	MLH1 (CGI)	2%			[111]
	MSH2 (CGI)	13%	*MSH2*	5%	
	MGMT (CGI)	47%	*MGMT*	11%	
	ERCC1	100%	*ERCC1*	40%	[112]
	PMS2	88%	PMS2	50%	
XPF	55%	XPF	40%		
Gastric	*MGMT* (CGI)	88%	*MGMT* (CGI)	29%	[113]
	WRN (CGI)	25%			[2]
Esophageal squamous cell carcininoma	*MLH1* (CGI)	49%			[114,115]
	MLH2 (CGI)	35%			
	MGMT (CGI)	41%			
Larynx	*MGMT* (CGI)	54%	*MGMT* (CGI)	38%	[116]

Cancer	Epigenetic changes in cancer (mechanism)	% sporadic cancers with epimutations	Epigenetic changes in field defect (mechanism)	% field defects with epi-mutations	Ref.
Non-small cell Lung	*WRN* (CGI)	38%			[2]
	MGMT (CGI)	70%	*MGMT* (CGI)	40%	[117]
Prostate	*WRN* (CGI)	20%			[2]
Thyroid	*WRN* (CGI)	13%			[2]
Non-Hodgkin lymphoma	*WRN* (CGI)	24%			[2]
Leukemias	*WRN* (CGI)	5-10%			[2]
Chondrosarcomas	*WRN* (CGI)	33%			[2]
Osteosarcomas	*WRN* (CGI)	11%			[2]
Brain glioblastoma	*MGMT* (CGI)	51%			[118]
	MGMT (miRNA)	28%			[78]
Liver hepatocellular carcinoma	*P53* (non-CGI promoter site specific methylation)	100%			[119]
Papillary thyroid (tested 23 DNA repair genes for CGI)	*MLH1* (CGI)	21%			[120]
	PCNA (CGI)	13%			
	OGG1 (CGI)	2%			

*CGI=CpG island methlyation

Table 7. Examples of epigenetic alterations (epimutations) of DNA repair genes in cancers and in field defects, with mechanisms indicated where known.

Deficiencies in DNA repair genes cause increased mutation rates. Mutations rates increase in MMR defective cells [81, 82] and in HRR defective cells [83]. Chromosomal rearrangements and aneuploidy also increase in HRR defective cells [84]. Thus, deficiency in DNA repair causes genomic instability and genomic instability is the likely main underlying cause of the genetic alterations leading to tumorigenesis. Deficient DNA repair permits the acquisition of a sufficient number of alterations in tumor suppressor genes and oncogenes to fuel carcinogenesis. Deficiencies in DNA repair appear to be central to the genomic and epigenomic instability characteristic of cancer.

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Figure 3 illustrates the chain of consequences of exposure of cells to endogenous and exogenous DNA damaging agents that lead to cancer. The role of germ line defects in DNA repair genes in familial cancer are also indicated. The large role of DNA damage and consequent epigenetic DNA repair defects leading to sporadic cancer are emphasized. The roles of germ line mutation and directly induced somatic mutation in sporadic cancer are indicated as well.

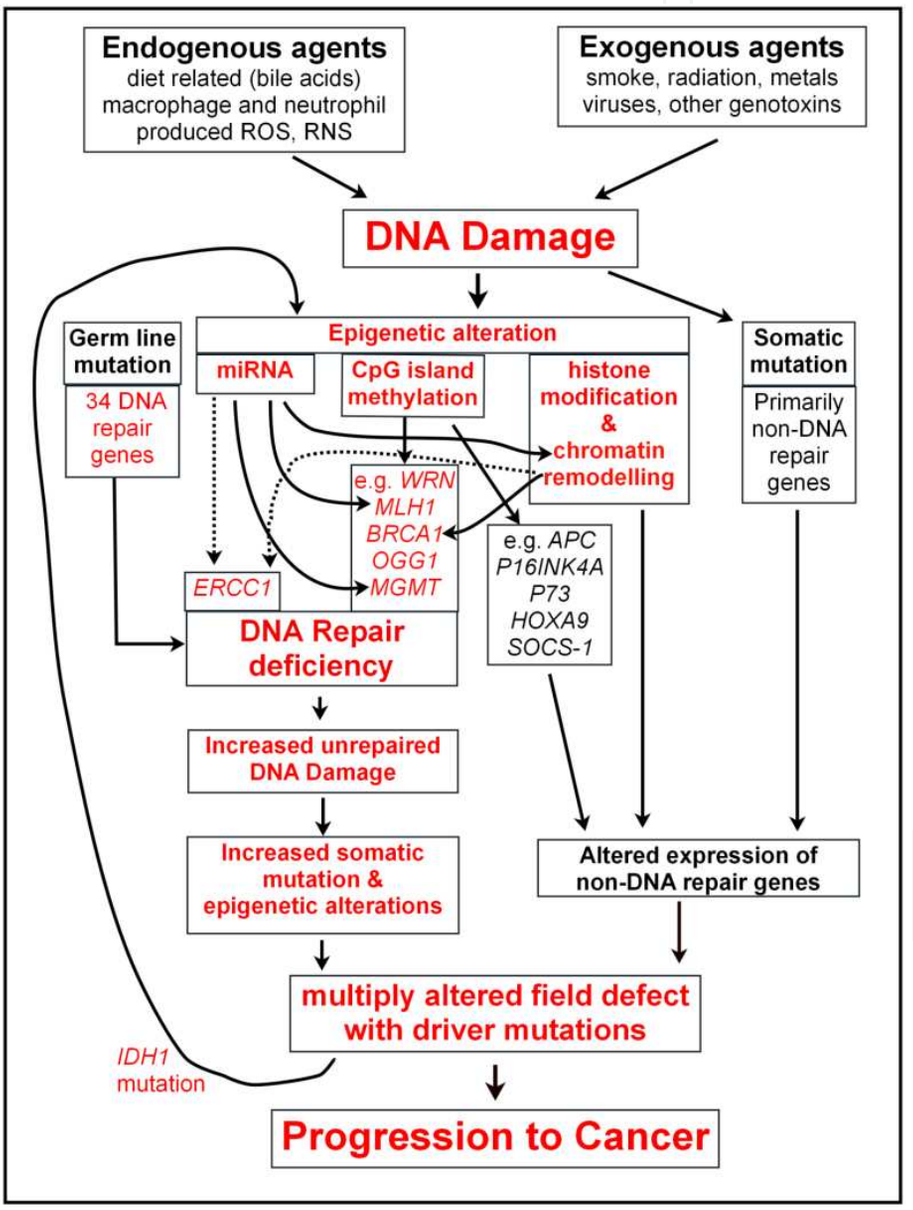

Figure 3. The roles of DNA damage, epigenetic deficiencies in DNA repair and mutation in progression to cancer.

11. Epigenetic alterations caused by micro RNAs

MicroRNAs (miRNAs) are endogenous non-coding RNAs, 19-25 nucleotides in length, that can have substantial effects on DNA repair. miRNAs can either directly or indirectly reduce expression of DNA repair or DNA damage response genes. As discussed above, over-expression of miR-155 causes reduced expression of DNA repair protein MLH1, and miR-155 is overexpressed in colon cancers [77] (curved arrow in Figure 3). Similarly, miR-181d is overexpressed in glioblastomas, causing reduced expression of DNA repair protein MGMT [78]. Although miRNAs can epigenetically regulate DNA repair gene expression, the expression levels of many miRNAs may themselves be subject to epigenetic regulation. One mechanism of epigenetic regulation of miRNA expression is hypomethylation of the promoter region of the DNA sequence that codes for the miRNA. Schnekenburger and Diederich [7] list miR-155 as one of a long list of mi-RNAs whose expression is increased by hypomythylation in colorectal cancers. In particular, hypomethylated miR-155 (the hypomethylation making it more active) targets genes *MLH1, MSH2* and *MSH6,* causing each of them to have reduced expression [7].

Wan et al. [121] referred to 6 further DNA repair genes that are directly targeted by miRNAs. *ATM, RAD52, RAD23B, MSH2, BRCA1* and *P53*, are each specifically targeted by one or two of the 8 miRNAs miR-21, miR-24, miR-125b, miR-182, miR-210, miR-373, miR-421 and miR-504, with all but miR-210, miR-421 and miR-504 among those identified by Schnekenburger and Diederich [7] as overexpressed through epigenetic hypomethylation. Overexpression of any one of these miRNAs leads to reduced expression of its target DNA repair gene. Wan et al. [121] further listed 16 DNA damage response genes targeted by specific miRNAs. Wan et al. [121] indicated miR-15a, miR-16, miR-17, miR-20a, miR-21, miR-24, miR-29, miR-34a, miR-106a, miR-93, miR-124a, miR-125b, miR-192, miR-195, miR-215, miR-182, miR-373 as among those targeting DNA damage response genes. Of these, all but miR-124a were identified by Schnekenburger and Diederich [7], (and Malumbres [122] further identified miR-34a and miR-124a) as being among miRNAs whose expression is subject to epigenetic alteration in tumors. Other miRNAs whose expression is subject to epimutation in colorectal cancers (and their target DNA repair or DNA damage response genes) include miR-17 (*E2F1*), miR-34b/c (*P53*), miR-106a (*E2F1*), miR-200a and miR-200b (*MLH1, MSH2*) and miR-675 (*Rb*) [7].

12. Epigenetic alterations caused by chromosome remodeling and histone modification

Specific miRNAs can also indirectly (and strongly) reduce protein expression of DNA repair genes through their role in repression of proteins designated High Mobility Group A1 (HMGA1) and HMGA2 (the names come from the proteins' high electrophoretic mobility on acrylamide gels). HMGA1 and HMGA2 cause chromatin remodeling at specific sites in DNA and reduce expression at those sites. In particular, these proteins appear to control

DNA repair genes *BRCA1* and *ERCC1*. BRCA1 And ERCC1 proteins have key roles in DNA repair, particularly of double-strand breaks and interstrand crosslinks. *HMGA1* and *HMGA2* genes are usually active in embryogenesis, but normally have very low expression levels in adult tissues. Their expression levels in adult tissues are kept low by the actions of specific miRNAs. If expression of these miRNAs is reduced, then the repressive HMGA1 and HMGA2 proteins become highly expressed and, in particular, can reduce expression of *BRCA1* or *ERCC1* respectively.

As reviewed by Resar [123], all HMG proteins share an acidic carboxyl terminus and associate with chromatin. As an example, HMGA1A, in particular, has three AT-hook domains that allow it to bind to AT-rich regions and recruit an "enhanceosome" that may displace histones and cause chromosome remodeling and reduce gene expression. Baldassarre et al. [124] showed that HMGA1B protein binds to the promoter region of *BRCA1* and inhibits *BRCA1* promoter activity (indicated in Figure 3 as chromatin remodeling causing reduced *BRCA1*). In 12 surgically removed human breast carcinomas, there was an inverse correlation between HGMA1 protein and *BRCA1* mRNA levels. HGMA1 was almost undetectable in normal breast tissue, highly expressed in the tumor samples, and BRCA1 protein was strongly diminished in tumor samples. Baldassarre et al. [124] suggested that while only 11% of breast tumors had hypermethylation of the *BRCA1* gene, 82% of aggressive breast cancer specimens have low BRCA1 protein, and most of these could be due to chromatin remodeling by high levels of HMGA1 protein.

Similarly, HMGA2 binds to an *ERCC1* promoter site and represses *ERCC1* promoter activity [125]. The miRNAs miR-23a, miR-26a and miR-30a inhibit *HMG2A* protein expression [126] though it has not been reported whether these miRNAs are under epigenetic control. In Figure 3, one of two dotted lines is used to indicate possible repression of *ERCC1* by epigenetically induced chromatin remodeling.

Resar [123] and Baldassarre et al. [124] summarized reports indicating that *HGMA1* is widely overexpressed in aggressive malignancies including cancers of the thyroid, head and neck, colon, lung, breast, pancreas, hematopoetic system, cervix, uterine corpus, prostate and central nervous system. Palmieri et al. [127] showed that *HGMA1* and *HMGA2* are targeted (and thus strongly reduced in expression) by miR-15, miR-16, miR-26a, miR-196a2 and Let-7a. The promoter regions associated with miR-16, miR-196a2 and Let-7a miRNAs are epimutated by hypomethylation [7, 122] while Sampath et al. [128] showed, in addition, that the coding regions for miR-15 and miR-16 were epigenetically silenced due to histone deacetylase activity. Palmieri et al. [127] further showed that these 5 miRNAs are drastically reduced in a panel of 41 pituitary adenomas, accompanied by increases in *HMGA1* and *HMGA2* specific mRNAs. In a more recent study on pituitary adenomas by D'Angelo et al. [129], reduced expression of 18 miRNAs was found, with 5 of them targeting *HMGA1* or *HMGA2*. In this recent study, among the 18 miRNAs with reduced expression, the reduced expression of miR-26b, miR-34b, miR-432 and miR-592 was known to be due to epigenetic alteration [7, 122]. Thus, epigenetic miRNA silencing, causing strong expression of *HMGA1* and *HMGA2*, occurs in many types of cancer and this may be related to reductions found in expression of DNA repair genes *BRCA1*, *BRCA2* and *ERCC1*.

Suzuki et al. [130], using genome wide profiling, found 174 primary transcription units for miRNAs, called "pri-miRNAs" (large precursor RNAs which may encode multiple miRNAs), of which they identified 37 as potential targets for epigenetic silencing. Of these 37 pri-miRNAs, 22 were encoded by DNA sequences with CpG islands (all of which were hypermethylated in colorectal cancer cells) while the other pri-miRNAs were subject to regulation by epigenetic "activating marks" without evidence of deregulated methylation.

Activating marks are alterations on histones that cause transcriptional activation of the genes associated with those altered histones (reviewed by Tchou-Wong et al. [131]). In particular, the nucleosome, the fundamental subunit of chromatin, is composed of 146 bp of DNA wrapped around an octamer of four core histone proteins (H3, H4, H2A, and H2B). Posttranslational modifications (i.e., acetylation, methylation, phosphorylation, and ubiquitination) of the N- and C-terminal tails of the four core histones play an important role in regulating chromatin biology. These specific histone modifications, and their combinations, are translated, through protein interactions, into distinct effects on nuclear processes, such as activation or inhibition of transcription. In eukaryotes, methylation of lysine 4 in histone H3 (H3K4), which interacts with the promoter region of genes, is linked to transcriptional activation. There is a strong positive correlation between trimethylation of H3K4, transcription rates, active polymerase II occupancy and histone acetylation. Thus trimethylation of H3K4 is an activating mark.

In addition to pri-miRNAs being regulated by activating marks, some miRNAs appear to be directly regulated by these histone modifications. As summarized by Sampath et al. [128], histone deacetylases catalyze the removal of acetyl groups on specific lysines around gene promoters to trigger demethylation of otherwise methylated lysine 4 on histones (H3K4me2/3) and this causes loss of these activating marks, promoting chromatin compaction, and leading to epigenetic silencing. Sampath et al. [128] showed that such histone deacetylase activity mediates the epigenetic silencing of miRNAs miR-15a, miR-16, and miR-29b. As indicated above, miR-15, miR-16 specifically target *HGMA1* and *HMGA2*. If miR-15 and miR-16 lose their activating marks, they have reduced expression, causing *HGMA1* and *HGMA2* to be transcriptionally activated, thus reducing expression of DNA repair genes *BRCA1* and *ERCC1*.

In Figure 3, histone modification and chromatin remodeling are indicated as epigentically altering the expression of many genes in progression to cancer, and specifically causing reduced *BRCA1* and possibly (as indicated by one dotted line) reduced expression of *ERCC1*. In addition, a second dotted line is used to indicate possible repression of *ERCC1* by an miRNA. Klase et al. [132] showed that a particular virally coded miRNA down regulates ERCC1 protein expression at the p-body level (a p-body is a cytoplasmic granule "processing body" that interacts with miRNAs to repress translation or trigger degradation of target mRNAs). A survey of human miRNA homology regions to *ERCC1* mRNA indicates at least 21 human coded miRNAs that could act to decrease *ERCC1* mRNA translation (shown in Microcosm Targets [133]). ERCC1 protein expression, assessed by immunohistochemical staining, is deficient due to an epigenetic mechanism in colon cancers [110], and this could be due to action of one or more miRNAs, acting directly on *ERCC1* mRNA.

13. Driver mutations and pathways to cancer progression

Recent research indicates a mechanism by which an early driver mutation may cause subsequent epigenetic alterations or mutations in pathways leading to cancer. Wang et al. [134] point out that isocitrate dehydrogenase genes *IDH1* and *IDH2* are the most frequently mutated metabolic genes in human cancer. A gene frequently mutated in cancer is considered to be a driver mutation [4] so that mutations in *IDH1* and *IDH2* would be driver mutations. Wang et al. [134] further point out that *IDH1* and *IDH2* mutant cells produce an excess metabolic intermediate, 2-hydroxyglutarate, which binds to catalytic sites in key enzymes that are important in altering histone and DNA promoter methylation. Thus, mutations in *IDH1* and *IDH2* generate a DNA CpG island methylator phenotype that causes promoter hypermethylation and concomitant silencing of tumor suppressor genes such as the DNA repair genes *MLH1, MGMT* and *BRCA1*. As shown in Figure 3, a driver mutation in *IDH1* can cause a feedback loop leading to increased DNA repair deficiency, further mutations and epimutations, and consequent accelerated tumor progression.

A study, involving 51 patients with brain gliomas who had two or more biopsies over time, showed that mutation in the *IDH1* gene occurred prior to the occurrence of a *p53* mutation or a 1p/19q loss of heterozygosity, indicating that *IDH1* mutation is an early driver mutation [135]. Work by Turcan et al. [136] showed that *IDH1* mutation alone is sufficient to establish the brain glioma CpG island methylator phenotype. Carillo et al. [137] showed that when an *IDH1* mutation was present in glioblastoma tumors, 64% of these were hypermethylated in the promoter regions of *MGMT*.

Other initial driver mutations can cause progression to glioblastoma as well. As pointed out above, increased levels of miR-181d also cause reduced expression of MGMT protein in glioblastoma. Nelson et al. [138] indicate that a single type of miRNA may target hundreds of different mRNAs, causing alterations in multiple pathways. Patients with a glioblastoma that does not harbor an *IDH1* mutation have an overall fairly short survival time, while patients with both mutated *IDH1* and methylated *MGMT* have a subtype of glioblastoma with a much longer survival time (implying a different pathway of cancer progression) [137].

An *IDH1* mutation that gives rise to a CpG island methylator phenotype that causes promoter hypermethylation and concomitant silencing of *MGMT* also causes promoter silencing of other genes as well. In addition to silencing of genes, the CpG island methylator phenotype can cause methylation of the promoter regions of long interspersed nuclear element-1 (LINE-1) DNA sequences. Ohka et al. [139] point out that LINE-1 is a class of retroposons that are the most successful integrated mobile elements in the human genome, and account for about 18% of human DNA. Ohka et al. [139] found that LINE-1 methylation is directly proportional to *MGMT* promoter methylation in gliomas and suggested that LINE-1 methylation could be used as a proxy to indicate the CpG island methylator phenotype status in glioblastomas. This phenotype, likely associated with methylation of the *MGMT* promoter, in turn, indicates whether treatment with the DNA alkylating agent temozolomide will be beneficial in treatment of a patient with a glioblastoma, since MGMT removes the alkyl groups added to guanine by temozolomide.

14. Field defects

Field defects have been described in many types of gastrointestinal cancers [140]. A field defect arises when an epimutation or mutation occurs in a stem cell that causes that stem cell to give rise to a number of daughter stem cells that can out-compete neighboring stem cells. These initial mutated cells form a patch of somewhat more rapidly growing cells (an initial field defect). That patch then enlarges at the expense of neighboring cells, followed by, at some point, an additional mutation or epimutation arising in one of the field defect stem cells so that this new stem cell with two advantageous mutations can generate daughter stem cells that can out-compete the surrounding field defect of cells that have just one advantageous mutation. As illustrated in Figure 4, this process of expanding sub-patches within earlier patches will occur multiple times until a particular constellation of mutations results in a cancer (represented by the small dark patch in Figure 4. It should also be noted that a cancer, once formed, continues to evolve and continues to produce sub clones. A renal cancer, sampled in 9 areas, had 40 ubiquitous mutations, 59 mutations shared by some, but not all regions, and 29 "private" mutations only present in one region [141].

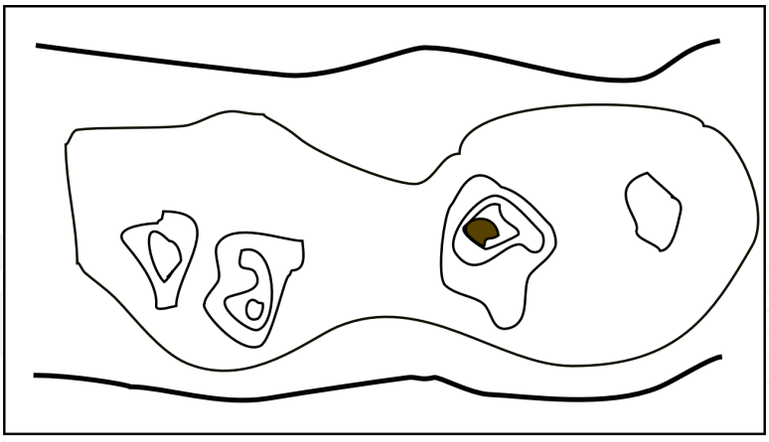

Figure 4. Schematic of a field defect in progression to cancer

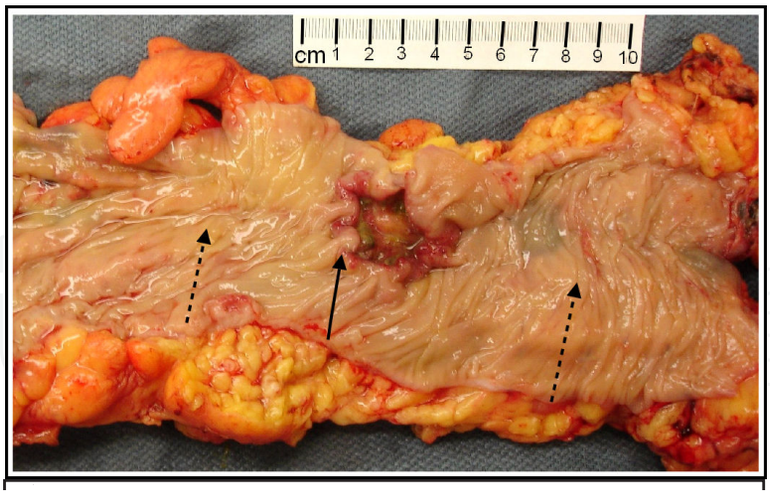

Figure 5. Colon resection including a colon cancer. Dashed arrows indicate grossly unremarkable colonic mucosa. Ulcerated hemorrhagic mass represents a moderately differentiated invasive adenocarcinoma. Solid arrow indicates the heaped up edge of the malignant ulcer

Figure 5 shows an opened resected segment of a human colon that has a colon cancer. As illustrated by Bernstein et al. [142], there are about 100 colonic microscopic epithelial crypts per sq mm in the colonic epithelium. The resection shown in Figure 5 has an area of about 6.5 cm by 23 cm, or 150 sq cm, or 15, 000 sq mm. Thus this area has about 1.5 million crypts. There are 10-20 stem cells at the base of each colonic crypt [143, 144]. Therefore there are likely about 15 million stem cells in the grossly unremarkable colonic mucosal epithelium shown in Figure 5. Evidence reported by Facista et al. [112], and listed in Table 7, indicates that in many such resections, most of the stem cells in such an area up to 10 cm distant (in each direction) from a colon cancer (such as in the grossly unremarkable area shown in Figure 5), and the majority of their differentiated daughter cells, are epigenetically deficient for protein expression of the DNA repair genes *ERCC1, PMS2* and/or *XPF*, although the epithelium is histologically normal.

The stem cells most distant from the cancer, deficient for *ERCC1, PMS2* and/or *XPF*, can be considered to constitute an outer ring, and be deficient as well in the inner rings, of a field defect schematically illustrated in Figure 4. The outer ring in Figure 4 includes, within its circumscribed area, on the order of 15 million stem cells, presumably arising from an initial progenitor stem cell deficient in DNA repair (due to epigenetic silencing). As a result of this repair deficit, the initial stem cell was genetically unstable, giving rise to an increased frequency of mutations in its decendents. One daughter stem cell among its decendents had a mutation that, by chance, provided a replicative advantage. This descendent then underwent clonal expansion because of its replicative advantage. Among the further decendents of the clone, new mutations arose frequently, since these descendents had a mutator phenotype [145], due to the repair deficiency passed down epigenetically from the original repair-defective stem cell. Among these new mutations, some would provide further replicative advantages, giving rise to a succession of more aggressively growing sub clones (inner rings), and eventually a cancer.

15. Exogenous carcinogenic agents cause reduced expression of DNA repair genes

Many known carcinogenic agents cause reduced expression of DNA repair genes or directly inhibit the actions of DNA repair proteins. Table 8 lists examples of carcinogens that have such effects. Due to space limitations, many other such carcinogens are not listed. These findings further link DNA damage to cancer.

Carcinogens	Inhibit DNA Repair Gene	Mechanism Shown	Ref.
Arsenic compounds	*PARP*		[146,147]
	XRCC1 *Ligase 3* *Ligase 4*		[146,148]
	DNA POLB, XRCC4 *DNA PKCS, TOPO2B*		[146]
	OGG1, ERCC1, XPF		[149]
	XPB, XPC, XPE		[150]
	P53	Inhibition of P53 serine 15 phosphorylation	[151]
Cadmium compounds	*MSH2, ERCC1, XRCC1* *OGG1*	Promoter methylation	[152]
	MSH2, MSH6 proteins	Cd^{2+} binds to proteins	[153]
	OGG1 protein	Oxidation of Ogg1	[154]
	DNA-PK, XPD		[155]
	XPC		[156]
Bile acids			
deoxycholate	*MUTYH, OGG1*	mRNA reduced	[157]
	BRCA1		[158]
lithocholate	*DNA POLB*		[159]
Lipid peroxidation compounds			
4-hydroxy-2-nonenal (4-HNE)	Nuc. Excision Repair	NER protein adducts	[160]
Malondialdehyde	Nuc. Excision Repair	NER protein adducts	[161]

Carcinogens	Inhibit DNA Repair Gene	Mechanism Shown	Ref.
Oxidative stress	MisMatch Repair	Oxidative damage to MMR proteins	[162]
	ERCC1 protein	Oxidative attack	[163]
	OGG1 protein	Degraded by calpain	[164]
Gamma irrad.	*OGG1, XRCC1*	mRNA reduced	[165]
Benzo(a)pyrene	*BRCA1*	miR-638 increased	[166]
Methylcholanthrene/ diethylnitrosamine	*BRCA1, ERCC1, XRCC1, MLH1*		[167]
Styrene	*XRCC1, OGG1, XPC*	mRNA reduced	[168]
Aristolochic acid	*P53, PARP1, OGG1, ERCC1, MGMT*	mRNA reduced	[169]
Antimony	*XPE*	mRNA reduced	[170]
Nickel	*MGMT*	Promoter methylation	[171]

Table 8. Examples of carcinogenic agents that cause reduced expression of DNA repair genes

16. Polyphenols can epigenetically increase expression of DNA repair genes

Some polyphenols affect expression of many genes, including DNA repair genes, through epigenetic alterations, as reviewed by Link et al. [172]. Examples of DNA repair genes expression increased by epigenetic alteration are listed in Table 9.

Phytochemical	Plant source	Mechanism	Targeted DNA Repair Genes	Ref.
Epigalocatechin-3-gallate	Green tea	Reversal of CpG island methylation	*MGMT, MLH1*	[173]
Dihydrocoumarin	Yellow sweet clover	p53 acetylation	*P53*	[174]
Genistein	Soy	Reversal of CpG island methylation	*MGMT*	[173]
Genistein	Soy	Histone acetylation	*P53*	[175]

Table 9. Examples of phytochemicals that increase expression of DNA repair genes by an epigenetic mechanism

17. Possible protection against cancer by phytochemicals that increase DNA repair by unknown mechanisms

A recent review article by Collins et al. [176] summarizes some examples of micronutrients that affect DNA repair gene expression, though by unknown mechanisms. Table 10 lists such phytochemicals, without defined mechanisms, that increase DNA repair gene expression, along with commonly known foods that are high in those phytochemicals [177, 178, 179].

Phytochemical (test system)	Examples of foods high in nutrient	Increased DNA Repair Gene Expression	Ref.
Ellagic acid (mice)	Raspberries, pomeganate	*XPA, ERCC5, DNA Ligase 3*	[180]
Silymarin (cells *in vitro*)	Artichoke, milk thistle	*MGMT*	[181]
Curcumin (cells *in vitro*)	Turmeric	*MGMT*	
Chlorogenic acid (cells *in vitro*)	Blueberries, coffee, sunflower seeds, artichoke	*PARP*	[182]
Caffeic acid (cells *in vitro*)	coffee, cranberry, carrot	*PMS2*	
m-coumaric acid (cells *in vitro*)	olives (and metabolite of caffeic acid)	*PARP, PMS2*	
3-(m-hydroxyphenyl) propionic acid (cells *in vitro*)	(major metabolite of caffeic acid and degradation product of proanthocyanidins in chocholate)	*PARP, PMS2*	

Table 10. Examples of phytochemicals that increase expression of DNA repair genes by unknown mechanisms

Bernstein et al. [182] evaluated antioxidants based on their ability to increase DNA repair proteins PARP-1 and Pms2 *in vitro*. They tested 19 anti-oxidant compounds and of these 19 compounds only chlorogenic acid and its metabolic products: chlorogenic acid, caffeic acid, *m*-coumaric acid and 3-(*m*-hydroxyphenyl) propionic acid, increased expression of the two tested DNA repair genes in HCT-116 cells (Table 10).

Chlorogenic acid (CGA) (high in blueberries, coffee, sunflower seeds, artichoke) [177, 183, 184] was then tested as a preventive agent in the recently devised diet-related mouse model of colon cancer [60]. As described above in the section Exogenous DNA damaging agents in colorectal cancer, deoxycholic acid (DCA), a DNA damaging agent, at levels present after a high fat diet, can cause colorectal cancer. When DCA is added to the diet of wild-type mice to raise the level of DCA in the mouse feces to the level in feces of humans on a high fat diet, by 10 months of feeding 94% of the mice develop tumors in their colons with 56% developing colonic adenocarcinomas [60]. This mouse model develops tumors solely in the colon, phenotypically similar to development of colon cancer in humans. When CGA, equivalent to 3 cups of coffee a day for humans, was added to the DCA supplemented diet it was dra-

matically protective against development of colon cancer, reducing incidence of colon cancer significantly from 56% to 18% [60].

18. Targeting of chemotherapeutic agents to cancers deficient in DNA repair

As discussed above, DNA repair deficiency often arises early in progression to cancer and can give rise to genomic instability, a general feature of cancers. If cancer cells are deficient in DNA repair they are likely to be more vulnerable than normal cells to inactivation by DNA damaging agents. This vulnerability of cancer cells can be exploited to the benefit of the patient. Some of the most clinically effective chemotherapeutic agents currently used in cancer treatment are DNA damaging agents, and their therapeutic effectiveness appears to often depend on deficient DNA repair in cancer cells.

In the next four sections we discuss repair deficiencies in cancer cells that can be effectively targeted by DNA damaging chemotherapeutic agents. In addition, deficiency in a DNA repair pathway that arises during tumor development may make cancer cells more reliant on a remaining reduced set of DNA repair pathways for survival. Recent studies indicate that drugs that inhibit one of these alternative pathways in such cancers cells can be useful in cancer therapy. Targeting cancer cells having a repair deficiency with specific DNA damaging agents, or with agents that inhibit alternative repair pathways, offers a new promising approach for treating a variety of cancers.

19. Targeting cancers deficient in BRCA1

The BRCA1 (breast cancer 1 early onset) protein is employed in an important DNA repair pathway, homologous recombinational repair (HRR). This pathway removes a variety of types of DNA damages, and is the only pathway that can accurately remove double-strand damages such as double-strand breaks and inter-strand cross-links. BRCA1 also has other functions related to preservation of genome integrity (reviewed by Yun and Hiom [185]). Individuals with a germ-line inherited defect in the *BRCA1* gene are at increased risk of breast, ovarian and other cancers. In addition to inherited germ-line defects in *BRCA1*, deficiencies in expression of this gene may arise in somatic cells either by mutation or by epimutation during progression to sporadic (non-germline) cancer.

Patients with a variety of types of cancer are treated effectively with chemotherapeutic agents that cause double-strand breaks (e.g. the topoisomerase inhibitor etoposide), or cause inter-strand cross-links (e.g. the platinum compound cisplatin). These damages can cause cancer cells to undergo apoptosis (a form of cell death). However, patients treated with these agents often prove to be intrinsically resistant, or develop resistance during treatment. Quinn et al. [186] demonstrated that BRCA1 expression is necessary for such resistance. This finding suggests that BRCA1-mediated DNA repair can protect cancer cells from therapeutic

DNA damaging drugs. Thus, although high expression of BRCA1 may be initially beneficial to the individual by reducing the risk of developing cancer, it also may be detrimental once cancer has developed by counteracting the therapeutic effect of DNA-damaging agents targeted to the cancer cells.

Patients with non-small cell lung cancer (NSLC) are often treated with DNA cross-linking platinum therapeutic compounds such as cisplatin, carboplatin or oxaliplatin. NSCLC is the leading cause of cancer deaths worldwide, and almost 70% of patients with NSCLC have locally advanced or metastatic disease at diagnosis. Improved survival after platinum-containing chemotherapy in metastatic NSCLC correlates with low BRCA1 expression in the primary tumor [187, 188]. This finding indicates that low BRCA1-mediated DNA repair is detrimental to the cancer upon treatment, and thus beneficial to the patient. BRCA1 likely protects cancer cells by participating in a pathway that removes the potentially lethal DNA cross-links introduced by the platinum drugs. Since low BRCA1 expression in the tumor appears to be beneficial to the patient, Taron et al. [187] and Papadek et al. [188] concluded that BRCA1 expression is potentially an important tool for use in cancer management and should be assessed for predicting chemosensitivity and tailoring chemotherapy in lung cancer.

Over 90% of ovarian cancers appear to arise sporadically in somatic cells and are associated with BRCA1 dysfunction. Weberpals et al. [189] showed for patients having sporadic ovarian cancer treated with platinum drugs, the median survival was longer for patients with lower expression of BRCA1 vs. higher BRCA1 expression (46 vs. 33 months).

20. Targeting cancers deficient in ERCC1

ERCC1 (Excision Repair Cross-Complementaion group 1) is a key protein needed to remove platinum adducts and repair inter- and intra-strand cross-links [190]. ERCC1 dimerizes with XPF (xeroderma pigmentosum complementation group F) protein to form a complex that can excise damaged DNA. Over-expression of ERCC1 is associated with cellular resistance to platinum compounds, whereas ERCC1 down-regulation sensitizes cells to cisplatin [191, 192].

Cisplatin has made a major impact in the chemotherapeutic treatment of testicular cancer. Over 90% of patients with newly diagnosed testicular germ cell cancer, and 70 to 80% of patients with metastatic testicular cancer, can be cured using cisplatin based combination chemotherapy [193]. Hypersensitivity of testicular cancer to cisplatin appears to be due to low levels of the three NER proteins ERCC1, XPF and XPA [194].

Simon et al. [195] evaluated ERCC1 mRNA expression in lung tumors as a predictor of survival of NSCLC patients. They found that patients with relatively low ERCC1 mRNA expression had poor overall survival. This finding suggests that low ERCC1-mediated DNA repair allows DNA damages to persist and give rise to carcinogenic mutations. However, they also noted that those NSCLC tumors with relatively low ERCC1 expression responded

better to platinum based therapy. Lord et al. [196] found that low *ERCC1* mRNA expression in the primary tumor correlates with prolonged survival after cisplatin plus gemitabine chemotherapy in NSCLC. Median overall survival with low ERCC1 expression tumors was 61.6 weeks compared to 20.4 weeks for patients with high expression tumors.

Zhou et al. [197] reported that a particular genetic polymorphism that alters ERCC1 mRNA level predicts overall survival in advanced NSCLC patients treated with platinum based chemotherapy. Olaussen et al. [198] found that patients with completely resected NSCLC tumors that were ERCC1-negative benefited from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors did not benefit. They suggested that determination of ERCC1 expression in NSCLC cells before chemotherapy can make a contribution as an independent predictor of the effect of adjuvant chemotherapy. Papadaki et al. [188] found that *ERCC1* mRNA level in the primary tumor of patients with metastatic NSCLC could predict the effectiveness of cisplatin based chemotherapy. Low *ERCC1* mRNA level was significantly associated with higher response rate, longer median progression-free survival and median overall survival. Leng et al. [199] found that patients with ERCC1 negative expression had a longer progression free survival and overall survival than ERCC1 positive patients after receiving platinum based adjuvant therapy. Thus *ERCC1* mRNA level, like *BRCA1* mRNA level (discussed above), in the primary tumor at the time of diagnosis could be used to predict platinum sensitivity of NSCLC.

ERCC1 expression also appears to have predictive significance for ovarian cancer. Dabholkar et al. [200] found in ovarian tumor tissues that *ERCC1* mRNA expression levels were higher in patients who were resistant to platinum based therapy than in those patients who responded to such therapy. Kang et al. [201] observed that a particular polymorphism of the ERCC1 gene sequence was associated with clinical outcome of platinum based chemotherapy in patients with ovarian cancer. Weberpals et al. [189] also showed for ovarian cancer patients that higher ERCC1 mRNA level, alone, or especially in combination with higher *BRCA1* mRNA level in the tumor, predicted shorter overall patient survival after platinum therapy.

ERCC1 protein expression is often reduced within colon cancers and in a field defect surrounding these cancers [112]. For metastatic colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy, lower *ERCC1* mRNA expression in the tumor predicts longer survival [202]. Viguier et al. [203] found that a particular ERCC1 genetic polymorphism predicts a better tumor response to oxaliplatin/5-fluorouracil combination chemotherapy in patients with metastatic colorectal cancer.

Low *ERCC1* mRNA levels also predict better response and survival for gastric cancer patients [204] and bladder cancer patients [205] receiving cisplatin-based chemotherapy.

Thus numerous studies involving cancer of the testis, lung, ovary, colon, stomach and bladder indicated that platinum based chemotherapy can enhance patient outcome when targeted specifically to tumors with low ERCC1 expression. Such tumors have diminished ability to repair the DNA damages, particularly the cross-links, induced in the tumors by the platinum compound.

21. Targeting cancers deficient in MGMT

Alkylating agents, including chloroethylnitrosoureas, procarbazine and temozolomide, are commonly used to treat malignant brain tumors. These agents cause DNA damage by adding alkyl groups to DNA. Such damages may then be repaired or, if unrepaired, trigger cell death. As an example, temozolomide methylates DNA at several sites generating mainly N^7-methylguanine and N^3-methyladenine adducts, which constitute nearly 90% of the total methylation events. However these adducts are efficiently removed and accurately replaced by the base excision repair pathway, and thus have low cytotoxic potential. About 5 to 10% of the methylation events caused by temozolomide produce O^6-methylguanine which is cytotoxic, and this adduct accounts for the beneficial therapeutic effect of temozolomide and other alkylating agents on malignant brain tumors.

O^6-methylguanine methyltransferase (MGMT) is a DNA repair enzyme that rapidly reverses alkylation (including methylation) at the O^6 position of guanine, thus neutralizing the cytotoxic effects of chemotherapeutic alkylating agents such as temozolomide. High MGMT activity in tumor tissue is associated with resistance to alkylating agents. MGMT activity is controlled by a promoter sequence, and methylation of the CpG island in the promoter silences the gene in cancer cells, so that these cells no longer produce MGMT. In addition, as described above, an increased level of miR-181d can also decrease MGMT expression and help the ability of temozolomide to give a beneficial therapeutic effect [78].

Esteller et al. [206] showed that methylation of the *MGMT* promoter increases the responsiveness of the gliomas (brain tumors) to chemotherapeutic alkylating agents, leading to regression of the tumors and prolonged overall and disease free survival. Paz et al. [207] showed that hypermethylation of CpG islands within the promoter sequence of the *MGMT* gene predicts a better clinical response to temozolomide in primary gliomas. They considered that their results might open up possibilities for more customized treatments of human brain tumors. Hegi et al. [208] demonstrated a significantly improved clinical outcome in patients with malignant glioma who had a methylated *MGMT* promoter and were treated with temozolomide. The 18-month survival rate was 62% among patients with a methylated *MGMT* promoter compared with only 8% in the absence of promoter methylation. Hegi et al. [209] reviewed further evidence that *MGMT* promoter methylation is associated with improved progression-free and overall survival in malignant glioma patients treated with alkylating agents. They also discussed strategies to overcome MGMT-mediated chemoresistance that are currently under investigation. Upon reviewing the relevant evidence, Weller et al. [210] concluded that *MGMT* promoter methylation is the key mechanism of *MGMT* gene silencing, and could be used as a biomarker for predicting a favorable outcome in patients with malignant glioma who are exposed to alkylating chemotherapy. They considered that this biomarker is on the verge of entering clinical decision-making.

22. Targeting cancers with a repair deficiency using a PARP inhibitor; synthetic lethality

If a tumor is deficient in an essential protein component of a DNA repair pathway, the cancer cells would likely be more reliant on remaining DNA repair pathways for survival. Drugs that inhibit one of these alternative pathways, in principle, might prove to be useful in cancer therapy by selectively killing the cancer cells. An example of such an approach is the use of poly(ADP-ribose) polymerase [PARP] inhibitors against tumors that are deficient in BRCA1 or BRCA2 [211]. This approach has provided proof-of-concept for an anticancer strategy termed "synthetic lethality." By this strategy the inhibition of a particular repair pathway in cancer cells that are already deficient in another repair pathway preferentially induces greater toxicity in repair deficient cancer cells than in normal non-cancer cells. Current research guided by this strategy is directed at finding new agents that inactivate protein components of major repair pathways, and thus could be targeted against cancers that are already deficient in another repair pathway [212].

A germ-line mutation in one *BRCA1* or *BRCA2* allele substantially increases the risk of developing several cancers, including breast, ovarian, and prostate cancer. Diploid cells heterozygous for either a *BRCA1* or a *BRCA2* mutant allele may lose expression of the remaining wild-type allele, resulting in deficient homologous recombinational repair. This loss causes an increase in unrepaired DSBs that can lead to mutations (through compensatory inaccurate repair) and chromosomal aberrations that drive carcinogenesis. Inactivation of the wild-type allele in the cell lineage leading to the tumor is thought to be an obligate step in this carcinogenesis pathway, a step that does not occur in the normal non-cancer tissues of the patient.

The deficiency in homologous recombinational repair is thus specific to the tumor, and can be exploited by employing PARP inhibitors. Ordinarily, single-strand breaks (SSBs), as distinct from DSBs, are repaired by the base excision repair pathway, in which the enzyme PARP1 plays a key role. The inhibition of PARP1 leads to the accumulation of DNA SSBs. Unrepaired SSBs can give rise to DSBs at replication forks during DNA replication. Thus PARP inhibition in tumor cells with deficient homologous recombinational repair (because of the absence of BRCA1 or BRCA2) generates unrepaired SSBs that are likely to cause an overwhelming accumulation of DSBs leading to tumor cell death. In contrast, the normal tissues of a patient consists of cells that are heterozygous for a *BRCA1* or *BRCA2* mutant allele and therefore retain homologous recombinational repair function, and have a sensitivity to PARP inhibitors similar to that of wild-type cells. Thus PARP inhibition induces selective tumor cell killing while sparing normal cells.

Fong et al. [213] conducted a preliminary clinical evaluation of the oral PARP inhibitor olaparib. They observed that 63% of patients carrying *BRCA1* or *BRCA2* mutations who had ovarian, breast or prostate cancer had a clinical benefit from treatment with olaparib with few adverse side effects. This is an example of the concept of "synthetic lethality" which occurs when there is a potent lethal synergy between two otherwise non-

lethal events. The two events in this case are (1) a specific PARP inhibitor blocks repair of SSBs causing an increase in SSBs leading to an increase in DSBs; and (2) a tumor restricted genetic loss of function or homologous recombinational repair that is ordinarily needed to accurately repair these DSBs.

A subsequent trial of olaparib in BRCA mutation-associated breast cancer demonstrated objective positive response rates of 41%, again with limited toxicity [214]. About 10% of women with ovarian cancer carry a *BRCA1* or *BRCA2* mutant allele. Audeh et al. [215] showed that the oral PARP inhibitor olaparib has antitumor activity in women carriers of *BRCA1* or *BRCA2* alleles who have ovarian cancer. The objective positive response rate was 33%.

23. Overview of the role of DNA damage and repair in carcinogenesis

In this section we present a brief overview of the relationship of DNA damage and repair to carcinogenesis, and the implications of this relationship for strategies of prevention and therapy, emphasizing the evidence reviewed above. Carcinogenesis is generally viewed as a Darwinian process that occurs in a somatic cell lineage by mutation or epimutation and natural selection. Natural selection operates on the basis of the adaptive benefit to individual cells in the lineage of more rapid cell division or higher resistance to cell death (apoptosis) than occurs in neighboring cells. Most of the random mutations and epimutations that arise during progression to cancer are likely to be disadvantageous or neutral from the prospective of the emerging cancerous cells, and only those that promote more rapid overall growth are advantageous. The cell lineage that ultimately becomes a cancer probably passes through a series of evolutionary pre-cancerous stages involving sequential rounds of mutation/epimutation and selection [216]. The initial stage is probably a lineage of cells with a small selective advantage that forms an early field within a tissue. Within this defective field successive mutation and selection events occur which finally give rise to an invasive and then metastatic cell lineage. During this process the cell lineage acquires the hallmarks of cancer (summarized by Hanahan and Weinberg [217]). These include: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, reprogramming energy metabolism, and evading immune destruction.

Mutations arise from unrepaired DNA damages, either by translesion synthesis during DNA replication or by inaccurate repair of DNA damages, as in the inaccurate process of non-homologous end joining of double-strand breaks. Mutations may also arise by spontaneous replication errors without the intervention of DNA damage, but this source of mutation is likely less frequent than mutations caused by DNA damage. The primary cause(s) of epimutations (such as CpG island methylations) are not well understood, but evidence suggests that epimutations arise during the repair processes that remove DNA damages. The sources of DNA damage underlying carcinogenesis can be extrinsic or intrinsic. Epidemiologic evidence suggests that a large proportion of the DNA damages contributing to cancer arise from extrinsic stressful conditions, including such factors as smoking, high fat diet, cer-

tain infections and UV light exposure. The possible contribution from intrinsic causes, such as free radical production during normal metabolism, have not been assessed. A pervasive characteristic of human tumors is genomic instability [217]. A likely major source of this instability is loss of DNA repair capability. Germ line mutations in DNA repair genes generally lead to syndromes characterized by a greatly increased risk of cancer. The majority of cancers arise sporadically, i.e. are not primarily due to germ line mutations. A frequent characteristic of sporadic cancers is loss of expression of one or more DNA repair proteins through epigenetic silencing. The several different DNA repair pathways that occur in mammalian cells each specialize in removing different types of damage, but they are also partially overlapping. Thus reduction of a particular repair pathway may have different carcinogenic consequences from loss of another repair pathway [218]. However, the deleterious effect of loss of one pathway may be partially ameliorated by another functioning pathway.

This general view of the role of DNA damage and repair in carcinogenesis has implications for the prevention and treatment of cancer. Cancer incidence could be substantially reduced by a general avoidance of the known sources of DNA damage such as smoking. In addition to avoiding DNA damage, it should also be beneficial to increase DNA repair, or at least to avoid extrinsic factors that decrease repair. The factors affecting repair capability are less well studied than those causing DNA damage, but several are known, and a significant benefit may be derived from considering such factors as well.

The finding that DNA repair deficiency is a common feature of cancers, and is perhaps the underlying cause of the genetic instability of cancers, has implications for therapy. If a cancer is composed of cells deficient in DNA repair, it is, in principle, vulnerable to agents that cause DNA damage. Thus a chemotherapeutic DNA damaging agent can be targeted to cancers that lack the capability to repair the particular type of DNA damage caused by the agent. This can lead to a level of DNA damages that overwhelms the defenses of the cancer cells and causes their death. Non-cancerous cells with normal repair would not be targeted. Thus the toxicity of such DNA damaging agents to the treated patient would be limited. A dramatic example of such targeted therapy is the high cure rate of testicular cancer due to a defect in the ability of the cancer cells to repair DNA inter-strand cross-links, and the use of cross-linking platinum compounds to kill such cells.

Another strategy, which is currently the basis for numerous ongoing clinical trials, involves synthetic lethality. By this strategy cancers that are deficient in one DNA repair pathway can be made more vulnerable to DNA damage by treatment with agents that inhibit an additional repair pathway. Promising clinical results, so far, have been obtained in the treatment of patients with breast and ovarian cancer due to an inherited genetic defect in the homologous recombinational repair pathway. Such cancers are deficient in the ability to repair double-strand breaks. Treatment of these cancers with an agent that interferes with another pathway that ordinarily repairs single-strand breaks allows such breaks to accumulate and to be converted to double-strand breaks during DNA replication. The increase in double-strand breaks appears to overwhelm the cancer cells, while sparing normal cells, thus providing positive clinical benefit to the patient without much toxicity.

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