DNA Damage, DNA Repair, and Mutagenesis

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GLOSSARY

carcinogen–DNA adducts Addition products that typically form as a result of covalent binding between a chemical carcinogen and a DNA base.

DNA damage Consists of (a) formation of carcinogen–DNA adducts and other chemical modifications of DNA bases and (b) alterations in DNA ultrastructure (DNA strand cross-links/DNA strand breaks/chromatid exchanges/chromosomal loss).

DNA mismatch mutations Unconventional base pairings, which can be *transitions* (purine to purine or pyrimidine to pyrimidine change resulting in two possible mispairings: G-T and A-C) or *transversions* (purine to pyrimidine or pyrimidine to purine resulting in six possible mispairings: A-A, C-C, G-G, T-T, A-G, or C-T).

DNA repair Consists of multiple different mechanisms for removing DNA damage from the genome and is a critical component in the maintenance of genomic integrity.

mutagenesis A permanent alteration in DNA structure that produces miscopying of information during DNA replication and yields abnormal gene products (proteins).

DNA damage consists of (a) formation of carcinogen–DNA adducts and other chemical modifications of DNA bases and (b) alterations in DNA ultrastructure (DNA strand cross-links/DNA strand breaks/chromatid exchanges/chromosomal loss). DNA damage can be induced by endogenous processes and by exogenous chemical and physical agents. A potential consequence of DNA damage is *mutagenesis*, i.e., a permanent alteration in DNA structure that produces miscopying of information during DNA replication and yields abnormal gene products (proteins). The process of carcinogenesis is considered to require mutations in multiple critical genes, and the risk of cancer is reduced when potentially mutagenic DNA damage is removed by DNA repair.

I. INTRODUCTION

DNA damage and the consequential mutagenic events are considered to bring about changes in gene expression that produce a loss of growth control, a clonal growth of cells, and ultimately a tumor. A substantial period of time is required for a tumor to become evident, and DNA damage is considered to be necessary but not sufficient for tumorigenesis, as other events, such as mutagenesis and cell proliferation, must also take place. DNA adduct levels, measured at any point in time, reflect tissue-specific rates of damage processing, which include carcinogen activation, DNA repair, adduct instability, tissue turnover, and other events. In experimental models, dose–response associations have been observed for DNA damage, mutagenesis, and tumorigenesis. Reductions in tumor incidences have been observed when DNA damage has been lowered, either by DNA repair processes or by administering compounds that inhibit DNA adduct formation (chemoprevention).

II. DNA DAMAGE

A. DNA-Damaging Agents

Agents that damage DNA can be either endogenous or exogenous, and they can be either direct acting or require metabolic activation. Arguably the most frequent endogenous mechanisms by which the integrity of DNA is compromised include deamination (cytosine or methylcytosine to form uracil or thymine) and depurination. The endogenous formation of reactive oxygen species and other free radicals, and exogenous exposure to irradiation (ultraviolet light, radon, X rays), can act to damage DNA directly producing cross-links, strand breaks, chromosomal aberrations, and other structural changes. Normal endogenous metabolic processes, e.g., lipid peroxidation, redox cycling, and endogenous nitrosation, can produce oxygen-free radicals, oxidative DNA adducts, etheno adducts, and nitrosamine adducts. Pathways that lead to the formation of oxygen radicals include degradation of organic peroxides (catechol, hydroquinone, and 4-nitroquinoline-*N*-oxide), hydrogen peroxide, lipid peroxidation, and the catalytic cycling of some enzymes. The role of endogenous nitric oxide is unclear because while there is the potential for oxyradical formation, nitric oxide is an effective scavenger of superoxide, resulting in nitrogen dioxide formation. Exposure to tumor promoters indirectly increases oxyradical formation; examples include the action of phorbol esters, mediated by protein kinase C, and inflammation mediated by nitric oxide. Oxygen free radicals produce multiple DNA adducts, including 8-hydroxy-deoxyguanosine, thymine glycol, 5-hydroxyuracil, 5-hydroxymethyl-uracil, and 6-hydroxy-5,6-dihydro-cytidine.

Exogenous (xenobiotic) DNA-damaging agents that are highly reactive and direct acting include radon, ultraviolet light, the nitrosoureas, some nitrosamines, ethylene oxide, and ozone. However, most exogenous chemical carcinogens are inert, such as the polycyclic aromatic hydrocarbons (PAHs), and require metabolic activation in order to become adducted to DNA. Inert exogenous agents are altered metabolically by families of enzymes that convert a small fraction of the initial dose to highly reactive intermediate metabolites that react directly with specific bases in nucleic acids. Examples of exogenous carcinogens are some plant and fungal products (aflatoxins, ochratoxins, hydrazines), pyrolysis products from cooking (heterocyclic amines, PAHs), industrial combustion products (aromatic amines, PAHs, nitro-PAHs, benzene, vinyl chloride, nitrosamines, ethylene oxide), urban pollution contaminants (PAHs, nitro-PAHs, aromatic amines), and contents of tobacco smoke (PAHs, nitosamines, aromatic amines). In addition, oxyradical formation may result from futile redox cycling that occurs through the metabolic activation of otherwise inert chemical carcinogens.

B. DNA Adduct Structures

There are a wide variety of DNA adduct structures, and some examples are shown in Fig. 1. Alkylation occurs when a portion of a chemical carcinogen, such as a methyl or ethyl moiety, becomes covalently bound to DNA. Alkyl radicals form during the metabolic activation of certain *N*-nitrosamines or spontaneously in the case of *N*-alkylureas (*N*-methyl-*N*-nitrosourea) and *N*-nitrosoguanidines. Protonated alkyl functional groups, which become available to modify DNA, attack nucleophilic centers on DNA bases. There are 10 of these: N1, N3, and N7 of adenine; N3 of cyto-

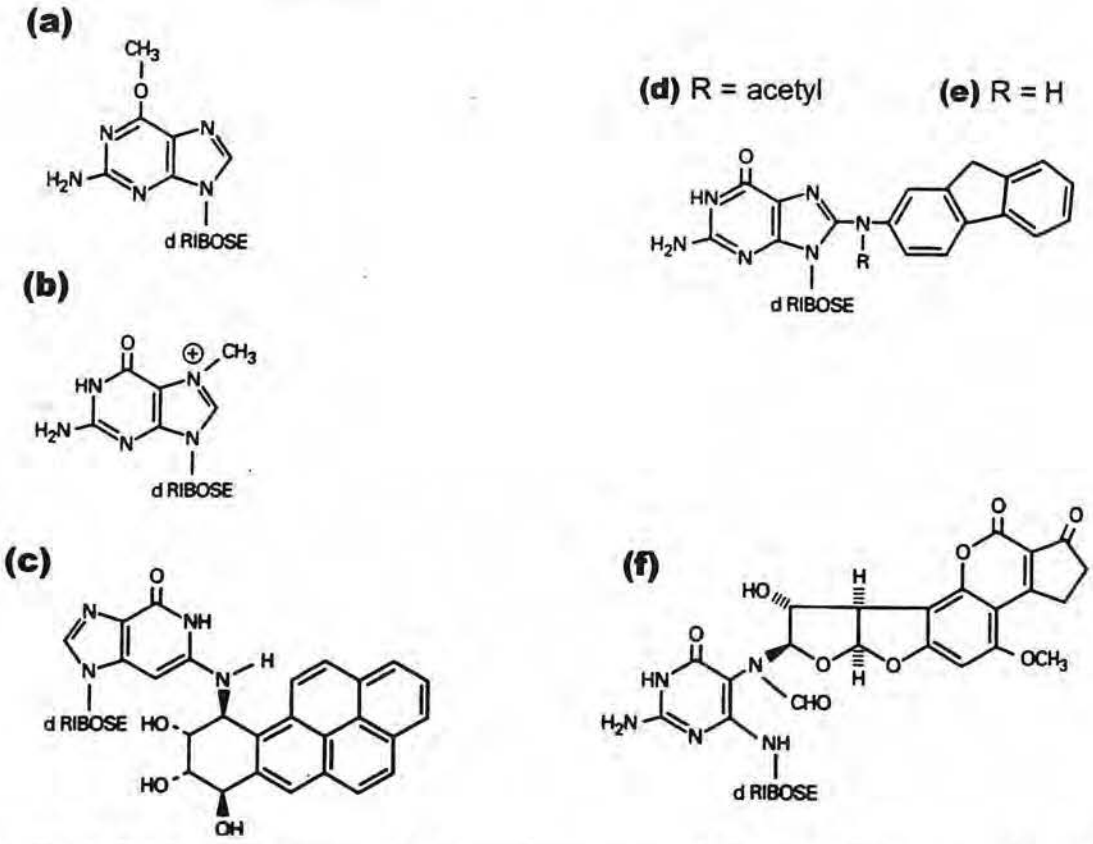

FIGURE 1 DNA adduct structures: (a) O^6-methyldeoxyguanosine; (b) N^7-methyldeoxyguanosine; (c) (7*R*)-N^2-(10[7β,8α,9α-trihydroxy-7,8,9,10-tetrahydro-benzo[α]pyrene]yl)-deoxyguanosine; (d) *N*-(deoxyguanosin-8-yl)-2-(acetylamino)fluorene; (e) *N*-(deoxyguanosin-8-yl)-2-(amino)fluorene; and (f) 8,9-dihydro-8-(N^5-formyl- 2′, 5′, 6′-triamino-4′-oxo-N^5-pyrimidyl)-9-hydroxy-aflatoxin B_1.

sine; N2, O6, and N7 of guanosine; and O2, N3, and O4 of thymidine. Repair of some of these lesions is correlated with mutagenicity; e.g., O6-methyldeoxyguanosine (Fig. 1a) can be repaired and is a promutagenic lesion, whereas N7-methyldeoxyguanosine (Fig. 1b) is neither repaired nor mutagenic.

Larger, aromatic-type ("bulky") DNA adducts are formed by covalent binding between the whole carcinogen molecule and DNA. The resulting three-dimensional structures reside either in the minor or in the major groove of the DNA helix and may cause distortion. Activated benzo[*a*]pyrene binds preferentially to the exocyclic (N2) amino group of deoxyguanosine (Fig. 1c). Guanine is a preferred site for modification by most PAHs, but covalent binding to deoxyadenosine and deoxycytosine is also possible. The major aromatic amine DNA adducts form at the C8 position of deoxyguanosine (Fig. 1d), but adducts are possible at the C8, N2, and O6 positions of deoxyguanosine and deoxyadenosine. Activation of aflatoxin B_1 produces adduction primarily at the N7 position of deoxyguanosine (Fig. 1e). As with smaller molecular weight adducts, the correlation among DNA adduct formation, mutagenicity, and DNA repair is not always predictable, and certain adducts appear to be more closely associated with mutagenicity than others.

C. Methods for DNA Adduct Determination

Methods currently used alone for carcinogen–DNA adduct detection include radiolabeling, immunoassays, immunohistochemistry, ^{32}P-postlabeling, fluorescence and phosphorescence spectroscopy, mass spectrometry, atomic absorbance spectrometry,

electrochemical conductance, and accelerator mass spectrometry. These methods work well for animal models where only one agent is under study, but in human tissues they are often unable to distinguish individual adducts, as multiple human exposures typically produce multiple DNA adducts. Success in the characterization of individual human DNA adducts has been obtained by combining preparative methods (immunoaffinity chromatography, high-performance liquid chromatography or gas chromatography) with immunoassays, ^{32}P-postlabeling, synchronous fluorescence spectrometry, or mass spectrometry. Most DNA adduct assays are able to detect as little as 1 adduct in 10^9 nucleotides using ~5–100 μg of DNA. Novel and sophisticated mass spectrometry-based methods have sensitivities similar to those found with more conventional assays, and accelerator mass spectrometry can detect 1 adduct in 10^{12} nucleotides but requires administration of exceedingly low levels of radioactively labeled compounds.

III. DNA REPAIR

The capacity for DNA repair, or removal of DNA damage, is a critical component in the maintenance of genomic integrity and stability. A diminished capacity for DNA repair is associated with carcinogenesis, birth defects, premature aging, and a foreshortened life span. There are six known basic DNA repair mechanisms: direct DNA repair, base excision repair, nucleotide excision repair, mismatch repair, homologous recombination, and nonhomologous end joining. In order to accomplish this range of DNA repair mechanisms cells employ complex protein–protein and protein–nucleic acid interactions. Hitherto, at least 125 genes have been implicated, either directly or indirectly in DNA repair. A list of human DNA repair genes, together with structural and functional information and potentially associated diseases, has been published.

A common thematic scenario, in the presence of genetic damage, is the implementation of cell cycle delay for the purpose of allowing DNA repair to take place. In this scenario, a damage recognition sensor triggers a signal transduction cascade and downstream effectors direct G_1 or G_2 arrest in concert with the proteins operationally responsible for the repair process. Although each repair mechanism is different, the DNA repair process is typically composed of some or all of several generic steps, which include damage recognition, damage removal or excision, resynthesis or patch synthesis, and ligation. These processes proceed efficiently because of the existence of multiprotein complexes comprising all of the machinery necessary to complete all of the DNA repair steps.

A. Direct DNA Repair

Alkyltransferases are suicide enzymes that commute alkyl groups from alkylated bases (O^6-methyldeoxyguanosine, Fig. 1a) to a cysteine residue. This process occurs in the active site in the enzyme in the absence of strand scission (Fig. 2a). One molecule of alkyltransferase is consumed during repair of one alkyl lesion in DNA; hence the term suicide enzyme.

B. Base and Nucleotide Excision Repair

Base and nucleotide excision repair processes are similar in that they both require strand scission, removal of a DNA segment containing the damaged base, reconstruction of the lost bases (repair patch), and ligation. A major difference is the size of the repair patch, which is about 3 bases in base excision repair and approximately 30–50 bases in nucleotide excision repair. The cell appears to choose one or the other based on the molecular size of the damage, as base excision repair is typically used to remove alkylation, whereas nucleotide excision repair is employed with large molecular weight ("bulky") carcinogens.

In base excision repair (Fig. 2bi), a glycosylase discards a damaged base, typically containing an adducted methyl, ethyl, or hydroxyl group. An apurinic endonuclease complexed with a 3′ repair diesterase displaces the glycosylase, degrading one to three bases on the damaged strand. The repair patch is typically synthesized by DNA polymerase β. Ligation is accomplished by one of a number of possible ligases that include *LIG1*, *LIG3*α, or *LIG3*β. An additional ligase variant, LIG 2, is formed through the proteolytic modification of LIG3.

Nucleotide excision repair (Fig. 2bii) proceeds by preincision lesion recognition, usually in response to

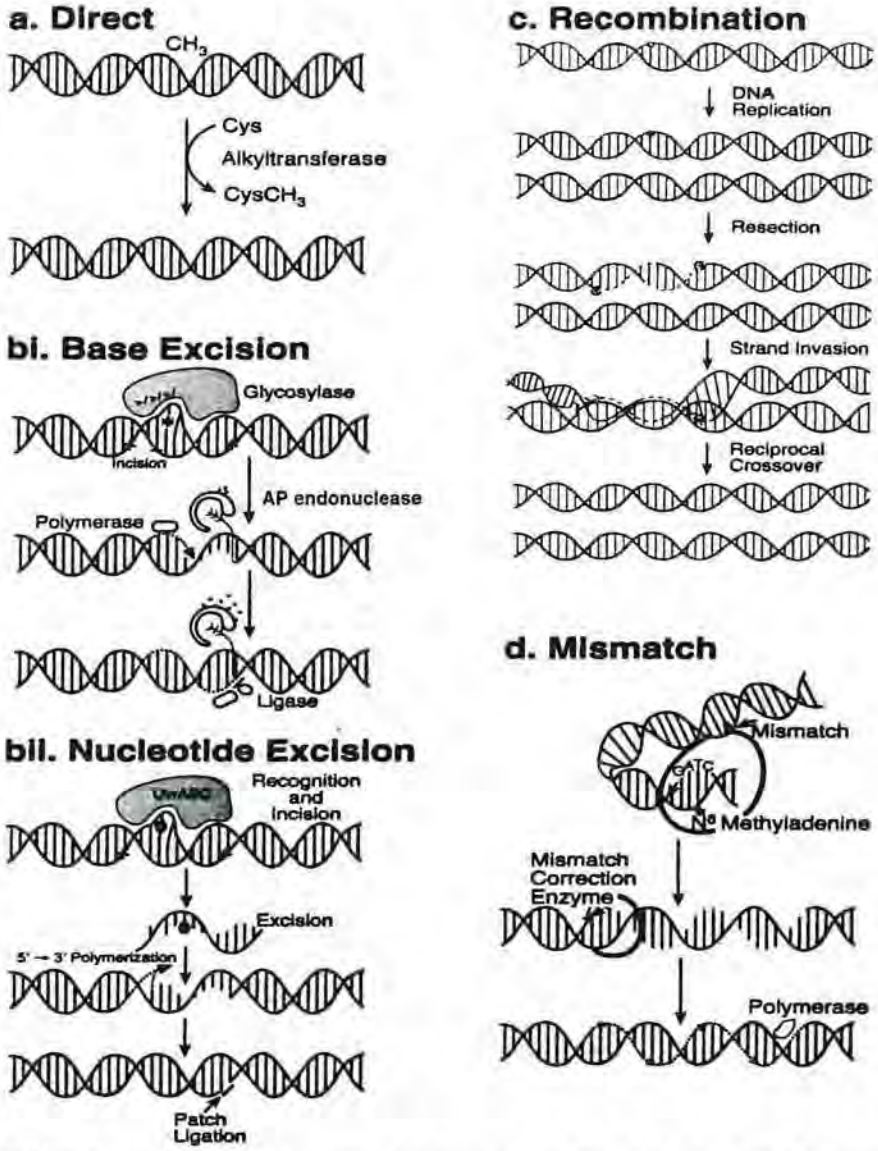

FIGURE 2 Mechanisms of DNA repair: (a) direct repair catalyzed by alkyltransferase; (bi) base excision repair, catalyzed by a glycosylase and an apurinic endonuclease; (bii) nucleotide excision repair, catalyzed by an endonuclease complex (e.g., UvrABC); (c) homologous recombination, catalyzed by a helicase complex; and (d) mismatch repair, catalyzed by a proofreading complex containing a correctional enzyme (e.g., hMLH1).

the formation of a bulky DNA adduct or ultraviolet damage (see Section II.B). Excinuclease complexes (e.g., UvrABC) are able to recognize such damage and excise a portion (30–50 bases) of the affected strand. For example, the XPC.RAD23 recognition complex recruits XPA.TFIIH to the repair location. An endonuclease, such as XPF, XPG, or FEN, clips out the damage. A 5′ - 3′ polymerase [e.g., polII activated through phosphorylation by CDK activating kinase (CAK), a member of the TFIIH complex] fills in the gap using the undamaged strand as a template. Ligation completes the closure at the 3′ junction. This type of DNA repair is generally strand specific, and the transcribed strand is preferentially repaired over the nontranscribed or non-DNA coding strand. In addition, transcribing regions of the DNA are

often repaired preferentially (transcription-coupled repair), compared to the whole genome (global genomic repair). Nucleotide excision repair is critical in humans. Loss of function of this pathway causes sensitivity to ultraviolet light, as evidenced in the clinic by the disease xeroderma pigmentosum. The clinical syndrome can involve loss of function of various proteins necessary for the nucleotide excision repair pathway, but all affected individuals experience early onset of skin cancer as a result of sun exposure.

C. Homologous Recombination and Postreplication Repair

Homologous recombination (Fig. 2c) occurs in response to DNA double strand breaks or the DNA damage tolerance mechanism known as postreplication repair. In postreplication repair, the replication polymerase either stops at the replication fork when DNA damage is detected or proceeds past the damaged base, leaving a gap. The gap can be filled with an adenine residue, potentially creating a mismatch (see Section III.D) or homologous recombination may occur. Thus, this mechanism is likely to introduce DNA sequence errors. Ionizing radiation, oxidative or mechanical stress, and some toxic chemicals can cause DNA double strand breaks, which also stimulate homologous recombination.

Homologous recombination is mediated by a helical nucleoprotein, such as the mammalian *RAD51*, which is homologous to *Rec*A of *Escherichia coli*. The first step involves simultaneous 5′ - 3′ resection of both strands catalyzed by a nuclease (e.g., nibrin complexed with RAD50/MREII). The 5′ tails of the disrupted DNA species invade the homologous duplex DNA and polymerization occurs using the appropriate, undamaged duplex strands as templates. Ligation and Holliday junction resolution occur on completion of polymerization through the action of an endonuclease. This can either result in a reciprocal crossover event or can be accomplished without crossover.

D. Mismatch Repair

DNA mismatches are unconventional base pairings, which can be transitions (purine to purine or pyrimidine to pyrimidine change resulting in two possible mispairings: G-T and A-C) or transversions (purine to pyrimidine or pyrimidine to purine resulting in six possible mispairings: A-A, C-C, G-G, T-T, A-G, or C-T). These can occur through mistakes in normal DNA repair processes or as a result of replication on a damaged template. For example, in postreplication repair (see Section III.C), the single nucleotide gaps that may be left are always filled by DNA polymerases with an adenine residue. This type of damage can also result from deamination of cytosine or 5-methylcytosine, which leaves a thymidine residue. Transversion mispairs are repaired more efficiently than transition mispairs, as a probable consequence of differential recognition.

Both nucleotide excision repair and mismatch repair have the common features that a large piece of the damaged strand is degraded and resynthesis occurs on the intact strand followed by ligation. However, a major difference is the mechanism of recognition (Fig. 2d). In mismatch repair the recognition protein complex (e.g., MLH1-MSH2-MSH6-PMS1 or MLH1-MSH2-MSH6-PMS2) binds simultaneously to the mismatch and the nearest unmethylated adenine in the recognition sequence GATC. The whole intervening strand sequence is excised, and the proliferating cell nuclear antigen can be recruited as a sliding clamp, providing a support for the action of DNA polymerases δ or ε. Ligation may be brought about by a ligase complexed to the polymerase (e.g., LIG1 complexes with polδ). This mechanism of DNA repair is critical in humans, and mutations in *hPMS1*, *hPMS2*, *hMLH1*, *hMLH2*, and *hMLH3* can predispose to cancers of the bowel and brain. Such mutations are relatively common, and 1 in ~200 persons are carriers.

E. Nonhomologous End Joining

Nonhomologous end joining is responsible for the repair of double strand breaks. This is a distinct but complementary mechanism to homologous recombination. The mechanism is homology independent because repair occurs without copying an undamaged template. Unless ligation of two complementary or blunt ends can restore the original sequence, a deletion mutation will result. Consequently, this mechanism is sometimes referred to as "illegitimate." The

process of nonhomologous end joining is mediated by XRCC4 and the DNA-dependent protein kinase holoenzyme. The site of a double strand break may be blunt or asymmetric. In the event of asymmetry, resection occurs with the purpose of creating a pair of blunt ends, which are then joined by LIG4 (XRCC4 is an essential cofactor for LIG4). Because nonhomologous end joining may require limited nucleotide degradation before ligation can occur, it is therefore error prone, leading to small deletions.

IV. MUTAGENESIS

A. Definition, Cause, and Evolutionary Importance

A mutation is a change in the sequence of DNA that results in alterations in the transcribed RNA and the translated protein (Fig. 3). Mutagenic DNA damage can be caused by endogenous and exogenous chemical and physical agents (see Section II.A) and typically consists of small molecular changes involving a few nucleotides (substitutions/insertions/deletions) or changes involving the gain or loss of large groups of nucleotides (large insertions/deletions/strand breaks/chromatid exchanges). Mutations can also occur as a result of cellular efforts to repair DNA (see Sections III.C, III.D, and III.E). During mutagenesis, structural changes in the DNA will result in the translation of proteins that have a loss of function, a gain of function, or no functional change. Mutagenesis is a major mechanism of evolution; typically mutations that lead to beneficial function will be selected for and others that lead to deleterious traits will be selected against.

B. Nature of Mutations and Mechanisms of Mutagenesis

Mutations involving small molecular changes consist of single base substitutions, as well as small insertions and deletions. Single base substitutions, missense mutations, are designated transitions if the original base and the new base are both either purines or pyrimidines (e.g., a G → A transition). However, a change from a purine to a pyrimidine or vice versa (e.g., G → T) is designated a transversion. Single base substitutions may have a rate of reversion similar to the original mutation rate. Insertions and deletions occur due to slippage and misrecognition by the polymerase, and such changes in the DNA structure may cause alterations in the DNA "reading frame," i.e., the sequence of nucleotides coding for a functional protein. For example, a normal reading frame contains signals for starting and stopping transcription that may be lost, and loss or gain of a critical amino acid in the coded protein may result in a change of catalytic activity. Mutations that change the reading frame of a protein are termed frameshift mutations.

Large DNA sequence rearrangements by recombination, chromatid exchange, or other copying errors can produce the accumulation of multiple mutations and genomic instability, as well as acceleration of the carcinogenic process. For example, large insertions and deletions can lead to chromosomal aberrations, and as the damaged cells attempt to divide, chromosomal DNA fragments can become translocated to unaccustomed positions and expressed inappropriately. Progressive genetic instability is a prominent feature of the carcinogenic process, resulting in the frequent occurrence of aneuploidy, gene amplification, microsatellite instability, chromosomal aberrations, and chromosomal loss in malignant tumors. The process of tumor progression appears to select for cells that are mutated in genes that function to ensure the stability of the genome, thus giving rise to the suggestion that most human cancers progress because they acquire a "mutator phenotype."

Mutagenesis has been dissected on a molecular level by site-specific studies in which an oligonucleotide carrying a specific damaged base or DNA adduct has been repaired by mammalian cultured cells and, after fixation, the resulting DNA mutations have been revealed by polymerase chain reaction and sequencing of the oligonucleotide target. Hemminki and colleagues have summarized mutagenic DNA adducts of various carcinogens elucidated by site-specific investigations. This type of study has demonstrated that the ability of an adduct to induce mutagenesis depends upon the DNA sequence context, the specific site that is modified on the base, the size and three-dimensional conformation of the modified base, conformational attributes of the adduct (tautomerization, ionization, rotation), and the polymerase involved.

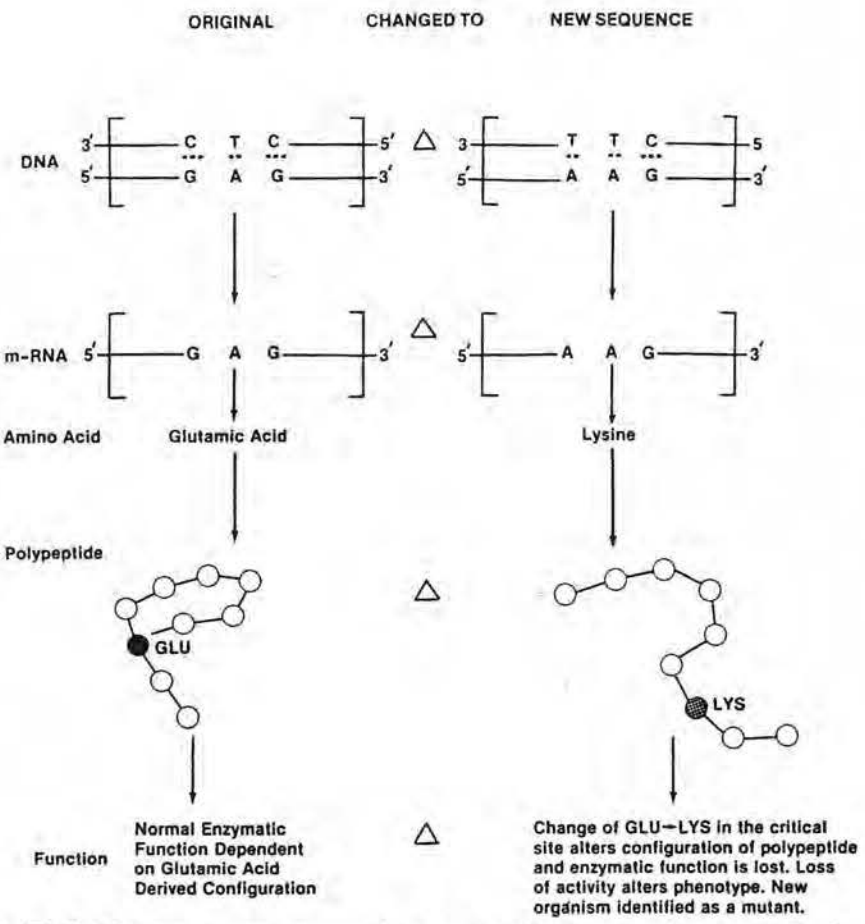

FIGURE 3 Schematic representation of a change in DNA sequence (CTC becomes TTC), which results in a miscoding of mRNA and a change in amino acid sequence (primary protein structure), whereby a glutamine residue is replaced by a lysine residue. This change in protein primary structure could lead to an alteration in protein folding and/or catalytic capacity.

Mutation "hot spots," or highly mutable sequences, have been observed in both site-specific mutagenesis and conventional mutagenesis assays and may occur for some of the reasons mentioned earlier. Frequently, a single carcinogen will produce multiple types of DNA adducts and mutations; however, it is occasionally possible to deduce the identity of a mutagenic DNA damaging agent by the mutations observed.

C. Measurement of Mutations

Mutations are typically measured in a specific target gene in cultured cells by growing mutagen-exposed cells in a selective medium that supports the growth of mutant but not normal cells, and growing normal cells in an optimal medium. Mutant frequencies are expressed as the number of mutated cell clones per 10^6 normal growing cell clones. Mutagen-induced reversion in the mutated histidine gene of *Salmonella typhimurium* comprises the basis of the Ames assay, which has been widely used to screen chemicals for potential genotoxicity.

In mammalian cells, a frequently investigated mutational target is the hypoxanthine–guanine phosphoribosyl–pyrophosphate (*HPRT*) gene, which produces a protein involved in the incorporation of nucleotides into nucleic acids. Normal cells are selectively inhibited by the aberrant base analog 6-thioguanine, but cells that have a mutated HPRT enzyme grow well because the drug is not incorporated into

nucleic acids. In addition to experimental models, *HPRT* mutagenesis in human peripheral T-cell lymphocytes is frequently used as a human biomarker, and studies in the general population show that the individual burden of *HPRT* mutations increases with age.

An additional human mutational biomarker is glycophorin A, a glycoprotein on the surface of red blood cells. Approximately 50% of the population are heterozygous, expressing both M and N alleles. The mutations scored are typically deletions of the M allele, which can be found by flow cytometry using specific antibodies. As the mutant clones persist, an age-related increase in glycophorin A mutant burden has been observed in the general population.

In addition to the classical methods for detecting mutagenesis, newer methods include sequencing-based molecular biology approaches and transgenic mice carrying the *Lac* locus. Mutations can be evaluated in any organ of a mouse carrying *Lac* as a target gene, as the locus can be packaged into a phage vector. After exposure of the whole mouse to a mutagen, DNA is extracted and cloned into the phage and mutations are determined by the clonal growth of colored colonies.

D. Mutations and Cancer

Mutations in the genes responsible for growth control allow uncontrolled clones of cells to become tumors. Hereditary cancers in children can be caused by mutations occurring in germline cells; however, somatic mutations occurring as a result of chemical or physical exposures will also destroy the normal cellular control of growth and cause cancer later in life. Typically, the critical target genes mutated in the process of tumorigenesis are protooncogenes and tumor suppressor genes. These genes have normal growth controlling functions; however, the mutated forms are activated oncogenes that have growth-enhancing properties and lost or inactivated tumor supressor genes that no longer have the capacity to control growth. Certain tumor supressor genes not only lose growth repression function, but can, in addition, gain oncogenic function; some *TP53* mutants are prone to this dual mechanism because their normal function involves transcriptional activation.

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Cancer in its many forms is one of the world's leading causes of death. Basic scientific research is slowly revealing a great deal about the causes of cancer and finding potential cures and preventive measures. This three-volume encyclopedia provides an overview of cancer research for medical practitioners; most articles will also be accessible to educated laypersons.

Editor in chief Joseph R. Bertino, chair of the Program of Molecular Pharmacology and Therapeutics at the Memorial Sloan Kettering Cancer Center, has assembled an international team of 297 scientists currently working in the field to write the 163 signed articles in the encyclopedia. The alphabetically arranged articles cover a wide range of subjects in the areas of molecular biology, genetics, pharmacology, radiation therapy, biology, and virology. Specific topics covered include *Cell cycle control*, *Multistage carcinogenesis*, *DNA damage*, *Mutation and repair*, and *Viral agents*. Each lengthy article has a table of contents, a glossary of terms, and a bibliography. Cross-references facilitate access to related material. Approximately 500 black-and-white and color illustrations and 250 tables augment the text.

Each volume contains two tables of contents for the entire set: an alphabetical list and a subject area list that arranges entries by broad topic. There is also a detailed index with more than 10,000 entries. A 1,500-term glossary completes the set.

The *Encyclopedia of Cancer* is unique because of its multidisciplinary approach to cancer. Most biomedical sources emphasize the clinical aspects of the disease. While it will not help patients make treatment decisions, it will tell them about current scientific research that may lead to new regimens. The *Encyclopedia of Cancer* is an essential source for biological and health sciences collections. Large public libraries with sufficient funds will want to consider it, too. --*This text refers to the Hardcover edition.*

From Book News, Inc.

Since cancer is the second biggest killer in the US next to cardiovascular disease, the voluminous research devoted to it demands an update to the first edition (1997). The editors' intent is not to provide detailed and comprehensive information but instead, concise exposition with cross-references and a bibliography for further study. All articles open with the author's occupational provenance, a table of contents, and a glossary. The second edition is in four volumes instead of the first... ▸read more

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