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DNA repair pathways and hereditary cancer susceptibility syndromes

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1. ABSTRACT

Every living organism is exposed to numerous genomic insults on a daily basis as a consequence of cellular metabolism and exposure to environmental agents capable of interacting with the genome (e.g. chemicals, toxins, pollutants, UV and ionizing radiation) (1). Maintenance of the integrity of the genome is paramount to the survival and propagation of a species and involves the continuous activity of a variety of DNA repair pathways. Inherited mutations in genes involved in DNA damage recognition and repair lead to disease by destabilization of the genome and increased mutagenesis. In fact, it is common for cancer cells to exhibit loss of genomic stability presumably as a result of clonally acquired mutations in DNA repair genes (2). Currently, roughly 150 DNA repair genes have been identified in humans (3) and a variety of familial cancer predisposition and/or premature aging syndromes are now linked to various loss-of-function mutations in these genes (4). Genetic interaction between DNA repair pathways and global cell differentiation pathways is supported by phenotypic similarities between inactivating mutations in a DNA repair, cell cycle arrest and apoptosis proteins. Though there is clearly some degree of functional redundancy between DNA repair pathways for correction of specific DNA lesions, the particular clinical characteristics of a repair defect can be predicted by the specific repair pathway affected (5). Patients with cancer predisposition syndromes often have multiple family members affected by cancer, develop cancer at an early age, and are at risk for developing multiple primary tumors over time (6, 7). Though patients with identifiable cancer predisposition syndromes are rare, defining their molecular defects has led to widespread applicability by uncovering relevant molecular pathways that are perturbed via somatic (non-inherited) mutations in the majority of sporadic cancers. In this review, we describe general molecular mechanisms of major forms of DNA repair and illustrate clinical consequences of deficiencies in these pathways. For more in depth detail, the reader is referred to several recent reviews and texts (2, 8-13).

2. INTRODUCTION

Disposable biomolecules such as proteins, lipids or RNA have a discreet half life and are generally replaced when defective. In contrast, DNA must be repaired when damaged (14). To that end, cells have evolved complex molecular pathways to both detect DNA damage and to pause cell replication (to allow for repair) to maintain genomic integrity. If left unrepaired, DNA damage can interfere with transcription, arrest proliferation and trigger apoptosis (15, 16). DNA damage can cause genetic mutations, permanent base changes in the sequence of nucleotides of DNA (11). Since we know that mutation(s) in critical genes are needed for oncogenesis, it follows that molecular predisposition to mutagenesis (as might occur through defective repair processes) promotes mutagenesis and neoplasia, and accumulation of mutations over time may also contribute to the aging process (17). DNA damage-sensing and -repair pathways exist in organisms across the phylogenetic spectrum to maintain genetic homeostasis, and pathologic disease results when such mechanisms are lost (3). Even in lower organisms, more than 100 genes are known to be involved in DNA damage recognition and repair, emphasizing the biologic importance of these pathways (2). In fact, most mutations are probably neutral, occurring in irrelevant non-coding, non-regulatory regions of the genome. However, those that affect coding regions or regulatory elements of vital genes (including DNA repair genes) may harm the cell (18). Changing the amino acid sequence of a protein product can radically change enzymatic function, cellular localization and/or intermolecular binding interactions (19), and since genes have evolved under constant selective pressure toward optimal function, most mutations that alter protein structure, quantity or function will result in a net negative influence at the cellular or organismal level. If loss-of-function mutations occur in key regulatory genes vital for proliferation and survival, cell growth can become autonomous and lead to malignant transformation (20). Between four and seven mutations in separate key pathways seem to be required for the development of full-blown cancer (21-24) and loss of key DNA repair pathways may accelerate tumorigenesis by predisposing cells to further genetic changes (13, 25, 26). Loss of effective DNA repair and/or chromosomal instability is noted in the great majority of human tumors, a concept known as the "mutator phenotype" (13). Specifically, once a cell has lost DNA damage sensing or repair capacity, it can accrue further mutations without invoking protective apoptotic and cell cycle control checks (27). Since the development of cancer depends on the progressive acquisition of mutations in multiple cell pathways, a pro-mutagenic state (such as loss of effective DNA repair) might lead to neoplasia and other pathology (27, 28). The premature aging/progeroid symptoms noted with various DNA repair defective states may be related not to cumulative mutation load per se, but to cellular responses to unrepaired DNA damage. Recent work by Niedernhofer, et. al., for example, suggests that unrepaired damage induces an IGF1/insulin-mediated metabolic response that re-allocates organismal resources from growth to somatic preservation (7).

DNA is under constant assault from genotoxic agents that alter its structure. Even normal cellular metabolic processes cause alterations of nucleotide bases (e.g. deamination of cytosine into uracil) or loss of bases from the sugar-phosphate backbone through generation of free radicals, etc. (29). Furthermore, DNA reacts with a variety of physical and chemical agents in the environment that change chemical and molecular characteristics of bases (30). Altered bases tend to mispair with their normal Watson-Crick counterpart (e.g. A-T, G-C) and during replication, "incorrect" bases can be inserted by polymerases as a result. Cell division promotes the opportunity to incorporate a different nucleotide sequence into the genome of daughter cells (Figure 1). If DNA damage is left unrepaired before DNA synthesis occurs, new bases may be incorporated into the newly synthesized strand outside of normal Watson-Crick parameters, fidelity relative to the original base sequence may be lost, and newly synthesized strands may have a different sequence than parental strands (Figure 1) (11). Though the proteins and steps of DNA repair vary depending on the specific lesion, some generalities exist between molecular pathways. Chemical modification of nucleotide bases in DNA is frequently accompanied by abnormal molecular interactions (hydrogen bonding, etc.) between bases in complementary strands and alteration in the three dimensional structure of the DNA helix. This conformational change triggers recognition by cellular sensor proteins involved in DNA repair (31). After recognition of altered DNA structures, other repair enzymes are recruited to the lesion to correct the damage (32-37). The four major pathways of DNA repair are (1) nucleotide excision repair (NER) (38, 39), (2) base excision repair (BER) (40, 41), (3) mismatch repair (MMR) (16, 42, 43) and (4) recombinational repair (RR) (44, 45). In this review, we will describe basic types of DNA damage, give a summary of cellular repair processes and the clinical consequences that result when DNA repair is defective.

2.1. DNA Damage Response and Repair Pathways

Damage response proteins are called upon after genomic damage to activate repair pathways (46-49) and recruit DNA repair proteins to sites of DNA damage (50-53). Cells use a variety of protein kinases to amplify and transduce DNA damage signals including phosphoinositide-3-kinase-related proteins, ataxia-telangiectasia mutated (ATM) and ATM-Rad3-related (ATR) proteins (54), as well as the checkpoint kinases Chk1 and Chk2 and others (11, 35, 55-60). These protein kinases propagate the damage signal to global DNA damage mediators such as p53 and BRCA1 (55, 61-63) which regulate overall cellular processes such as proliferation and apoptosis. It is known from studying affected kindreds that defects in global damage response proteins clearly predispose affected individuals to cancer (6). The Li-Fraumeni syndrome (LFS) (64), in particular, is a highly-penetrant rare autosomal dominant condition caused by inactivating germline mutation in either the p53 tumor suppressor gene *TP53* or in the CHK2 kinase gene whose protein product activates p53 by phosphorylation after DNA damage (65, 66). Inactivation of p53 activity interferes with damage response signaling and allows

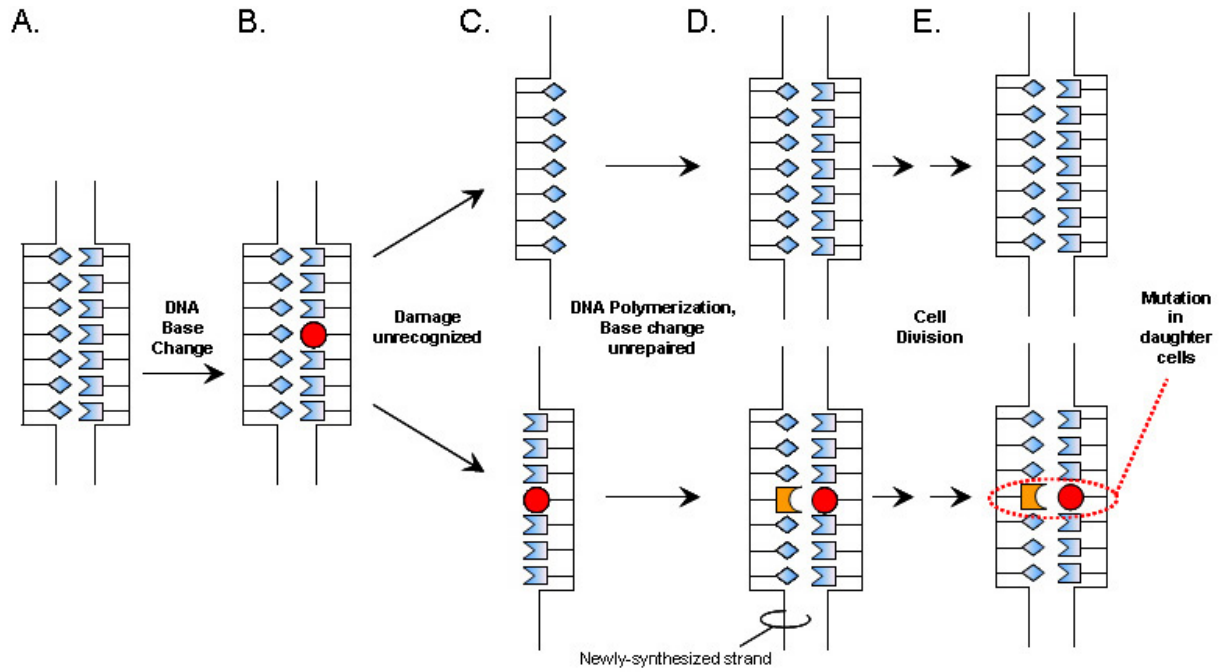

Figure 1. A simplified model of the heritability of mutation. A) In the normal, unaltered state, bases are matched according to Watson-Crick pairing rules (i.e. A:T and G:C). B) A nucleotide is altered, either by endogenous (oxidative metabolism, spontaneous deamination, etc.) or extracellular mutagens (carcinogen exposure, ultraviolet radiation, etc.). If this base alteration does not trigger effective DNA damage response and repair pathways and persists, then this change can become permanent in a subset of daughter cells through replication and cellular division (C-E).

Table 1. Clinical features of hereditary cancer syndromes

- Multigenerational involvement by cancers of a similar tumor type
- Characteristic tumors associated with hereditary cancer syndromes
- Early age at diagnosis (younger than average compared with the median age of diagnosis)
- Diagnosis of bilateral or multiple cancers or with multiple sites of primary tumors
- Constellation of physical findings or congenital anomalies consistent with specific cancer syndrome

cellular escape from p53-dependent apoptosis (67, 68). Individuals with LFS have a 50% cancer risk by age 40 and up to a 90% cancer risk by age 60 (69, 70). Genograms of LFS kindred families typically feature a high incidence of characteristic tumors (osteosarcoma, soft tissue sarcomas, leukemias, adrenocortical and breast carcinomas and brain tumors) over many generations, multiple primary tumors and uncharacteristically young ages of diagnosis (Table 1) (66, 69, 70). Besides its role in one inherited familial cancer syndrome p53 also plays a role in many cases of sporadic cancers, regardless of tumor type. In fact, somatic mutations in *TP53* are found in roughly fifty percent of *all human tumors* (71), highlighting the importance of DNA damage recognition in neoplastic resistance. Though damage recognition and control is critical in preventing neoplasia, our review will focus on actual DNA repair defects and known associated clinical cancer syndromes that result when such pathways are impaired.

2.2. Basic Types of DNA damage and their repair

2.2.1. Mismatched bases

DNA mismatch occurs when a non Watson-Crick base pair is created between nucleotides in opposing strands. This type of damage may occur during normal replication due to mistakes made by DNA polymerases, all of which demonstrate some degree of nucleotide infidelity. While most mismatch errors are immediately corrected by proofreading polymerase-associated exonucleases, mismatch repair (MMR) processes exist to correct mismatched bases that escape proofreading exonucleases (43).

2.2.2. Base loss and base modifications

The glycosyl bond linking DNA bases with deoxyribose is somewhat labile under physiological conditions.

When this bond breaks, the base is released from the sugar-phosphate backbone, the strand remains intact and an abasic site is formed (Figure 2). It is estimated that in this manner, the mammalian genome must cope with the loss of several thousand purines and several hundred pyrimidines per haploid genome each day (41). Production of abasic sites increases under conditions of oxidative stress (10) and cells have evolved effective repair pathways to correct such damage. Normally, the opposing undamaged strand serves as a template to direct incorporation of the missing nucleotide(s) by the base excision repair (BER) pathway.

In addition to bases being cleaved from the phosphodiester backbone, the amino groups of bases are

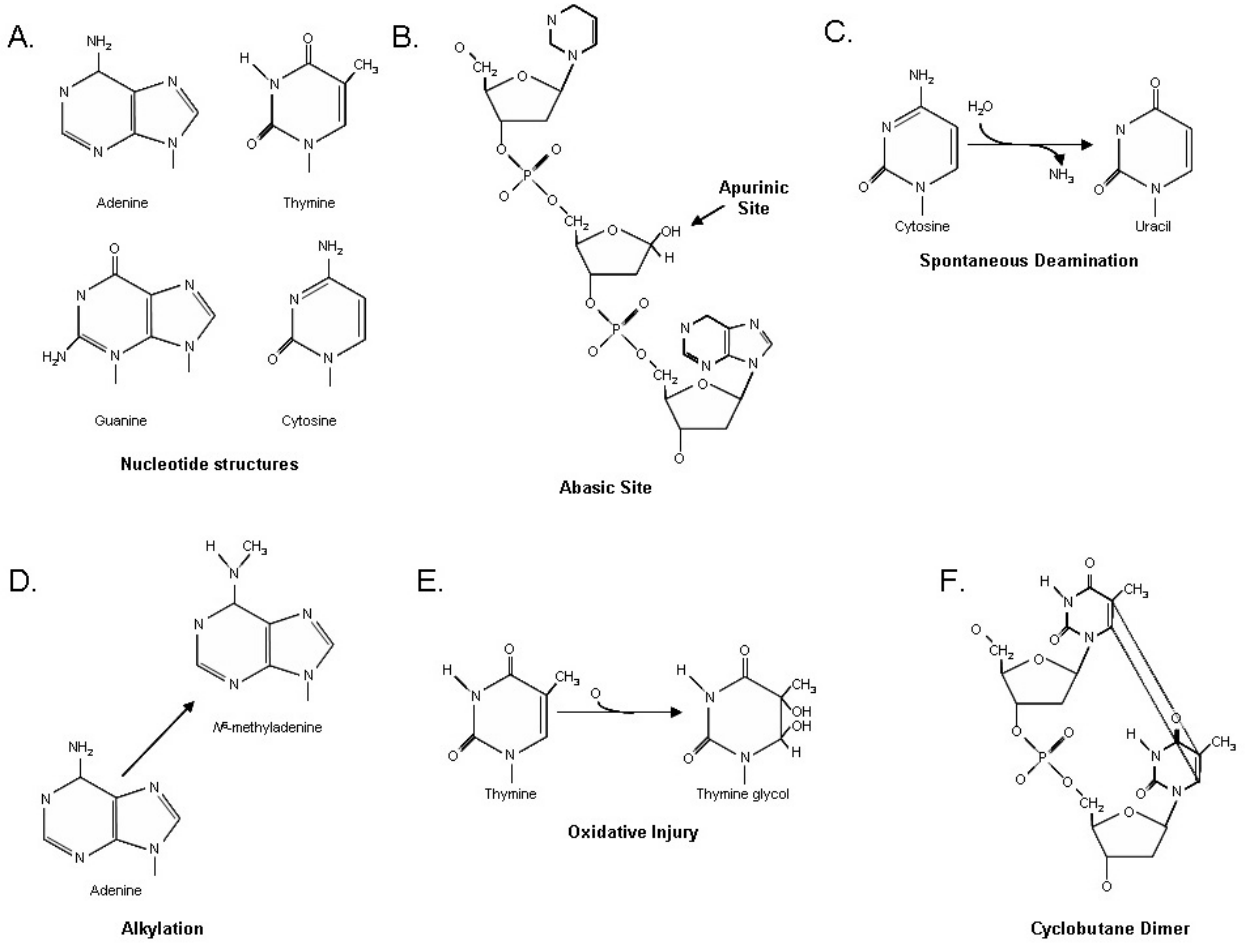

Figure 2. Nucleotide structures and examples of potentially mutagenic DNA lesions repaired by the cell. A) Structure of the 4 normal nucleotides found in DNA. B) Generation of abasic (apurinic) site by nucleotide base loss (note that the sugar-phosphate backbone remains intact and no strand breakage occurs, C) Spontaneous deamination (the most common form is conversion of cytosine to uracil), D) Alkylation of DNA through addition of bulky alkyl groups by chemicals such as ethyl methane sulfonate (nitrogen mustard gas) or a variety of alkylating chemotherapeutic agents, E) Base modification by oxidative injury and nucleotide interaction with oxidative free radicals, and F) Cyclobutane photo-dimer that forms between adjacent pyrimidines after exposure to photons in the UV-B or UV-C spectra.

vulnerable to spontaneous conversion to keto groups. In particular, uracil is frequently generated by spontaneous deamination of cytosine (Figure 2) and other base conversions similarly occur (e.g. adenine to hypoxanthine, guanine to xanthine, and 5-methyl cytosine to thymine). Methyl or other alkyl groups can be added to certain positions of nucleotide bases occurs through interaction with a variety of environmental chemicals. "Alkylation" can also occur as a result of normal metabolism. S-adenosylmethionine, for example, can donate a methyl group to adenine to produce 3-methyladenine. It is thought that many anti-cancer chemotherapeutic drugs function by promoting large-scale alkylation of DNA which then triggers apoptosis or disruption in cell proliferation in susceptible cells (72, 73).

Nucleic acid bases are susceptible to chemical modification by hyper-reactive oxygen species such as peroxide and hydroxyl radicals generated during normal oxidative metabolism or by exposure to oxidizing drugs or to radiation. Reactive oxygen species modify the chemical structure of DNA bases, converting thymine to thymine glycol (Figure 2) and causing a variety of other oxidative modifications (8-hydroxyguanine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine, 8-hydroxyadenine, 4,6-diamino-5-formamidopyrimidine, 5-hydroxyuracil and 5-hydroxy-cytosine) (74). The major oxidized purine lesion is 8-oxo-7,8-dihydroguanine (8-oxoG) which is abundant and mutagenic Dianov, 2001 #169; Nishigori, 2004 #985} by allowing the modified guanine to pair aberrantly with adenine (instead of cytosine). Thus, if 8-oxoG is left unrepaired before cell division occurs, a GC to TA transversion mutation can result (75). Beside risk of mutation, oxidized bases interfere with transcription and DNA synthesis and must be repaired to maintain genomic stability. Base modifications that tend not to cause significant DNA distortion such as those caused by oxidative damage are almost always corrected using the BER pathway (76-78).

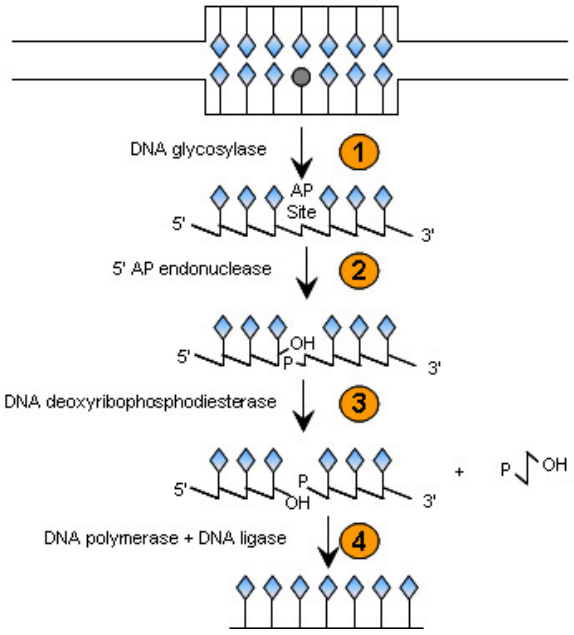

Figure 3. Base Excision Repair (BER). BER corrects single base changes using the opposing strand as a template for fidelity. DNA glycosylases scan the genome for specific base alterations (e.g. uracil). The damaged base is removed by hydrolysis of the N-glycosyl bond linking the base to the sugar-phosphate backbone (step 1), creating an abasic (apurinic) site in the DNA, which then attracts a 5' apurinic endonuclease whose enzymatic action results in a strand break with a 5' terminal deoxyribose-phosphate moiety (step 2) which is cleaved by a deoxyribophosphodiesterase resulting in a single nucleotide gap (step 3). DNA repair is completed by the actions of DNA polymerase and DNA ligase (step 4).

2.2.3. Photodamage

The double bond between the C5 and C6 of pyrimidine rings is sensitive to absorption and covalent modification by photons in the UV-B (290-320 nm) or UV-C (100-280 nm) ranges. Once these bonds are broken by direct absorption of the energy of UV light, abnormal covalent interactions can occur between neighboring pyrimidines that significantly alter the three-dimensional structure of the double helix (79). Cyclobutane dimers between adjacent thymidines and/or cytosines comprise the majority of photolesions after UV-exposure (Figure 2) (80) with pyrimidine [6,4]-pyrimidone photoproducts generated in lesser amount (81, 82). These covalent lesions distort the double helix and are clearly mutagenic, causing characteristic transitions known as "UV signature mutations". Photolesions are repaired mainly by the nucleotide excision repair (NER) pathway (38).

2.2.4. Strand breakage and crosslinks

Interstrand cross-links can be generated by bifunctional alkylating agents (e.g. psoralens) that chemically attach to nucleotide bases on both strands to form an abnormal trans-strand covalent link. UV and ionizing radiation can also generate interstrand cross-links (83, 84) and the double helix can also covalently interact with other macromolecules, such as DNA-protein crosslinks that occur during the course of topoisomerase enzymatic action. If reversal does not occur following topoisomerase enzyme activity, then a stable topoisomerase-DNA bond is established which prompts induction of cellular repair processes (85).

Strand breakage and discontinuity of the sugar-phosphate backbone can occur either in a single DNA strand (single-stranded break) or in both strands at the same location (double-stranded break). Both are potent triggers of cellular repair processes. Strand breaks occur at a low frequency during normal DNA replicative processes (e.g. with topoisomerase activity), but are generated at a much higher rate after exposure to ionizing radiation. Strand discontinuity is highly disruptive to the three-dimensional structure of the double helix, and must be repaired in a timely manner lest apoptosis triggering occurs (86). The cell uses non-homologous end joining (NHEJ) and recombinational repair (RR) to correct most double-stranded breaks, while single-strand breaks are most likely repaired by the BER pathway (86).

3. DNA REPAIR MECHANISMS AND SYNDROMES

3.1. Base Excision Repair (BER)

The BER pathway (Figure 3) is a highly conserved pathway utilized to repair DNA base damage that occurs from both endogenous and exogenous sources (87). The pathway recognizes and repairs base damage that causes minimal distortion to the DNA helical structure, including deaminated, alkylated bases, oxidized bases and abasic sites (40, 41, 88-90). The critical nature of the BER pathway is emphasized by the severe phenotypes observed in animals deficient in BER function, including genomic instability and premature aging (91) and severe metabolic disturbances (92). There are three basic steps to BER:

1. Recognition of altered or inappropriate bases by glycosylases that cleave abnormal nucleotides from the sugar moiety and phosphodiesterase backbone by hydrolysis of the N-glycosylic bond between the base and the deoxyribose, forming an abasic site.
2. Removal of the apurinic/apyrimidinic (AP) site by an AP-endonuclease or AP-lyase, which cleaves the DNA strand 5' or 3' to the AP site, respectively.
3. Excision of the remaining dexyribose phosphate residue by a phosphodiesterase, with correction of the resulting gap by a DNA polymerase and sealing of the strand by DNA ligase.

Unlike other types of repair that are triggered by physical distortion of the double helix, BER is initiated by one of at least eleven damage-specific, monofunctional or bifunctional glycosylases that scan the DNA for specific base alterations (40, 87, 89). A variety of mammalian N-glycosylases (UNG, SMUG, TDG, MBD4, MYH, OGG1, NTH1, NEIL1, NEIL2, NEIL3, and AAG) exist to recognize base defects and to initiate BER (87, 89). Many glycosylases recognize uracil in the double helix, the product of spontaneous deamination of cytosine and which occurs with some frequency. DNA glycosylases scan the

DNA and recognize positions of base-pair instability caused by mismatches with each glycosylase featuring binding sites for bases they are designed to recognize. If the base in question does not conform to an exact binding region in the enzyme, then BER may be initiated. Individual glycosylases may recognize several types of base modifications and individual types of damage may be recognized by more than one glycosylase, resulting in some degree of redundancy in the system. Some glycosylases are monofunctional, whereas others are bifunctional (having lyase activity in addition to glycosylase activity). Monofunctional glycosylases flip the damaged base into their active sites and then cleave the N-glycosylic bond between the base and the sugar phosphate backbone to release the damaged base. The resultant abasic site becomes the substrate for the next step in the pathway wherein an AP endonuclease incises the phosphodiester backbone to expose a 3' hydroxyl group and a 5' deoxyribose phosphate group which is repaired by either the short-patch or long-patch pathways. In the short-patch pathway, Pol beta in combination with the adapter protein XRCC1, synthesizes nascent DNA using the undamaged strand as a template to maintain fidelity. The deoxyribose phosphate group is removed and the nick in the DNA is then sealed by DNA ligase III. In the long-patch pathway, Poldelta/epsilon along with the adaptor proteins PCNA and RFC synthesizes new DNA two to six nucleotides beyond the abasic site, creating an overhang of oligonucleotides which is then shortened by the FEN1 Flap endonuclease followed by strand ligation by DNA ligase I (40, 89).

If BER is initiated by a bifunctional glycosylase, the enzyme flips the damaged base into its active site, but instead of cleaving the base from the sugar phosphate backbone, it removes the damaged base by nucleophilic attack. The resultant covalent intermediate phosphodiester bond is then cleaved by the enzyme's lyase activity 3' to the abasic site to generate a single strand break exposing a 3' 4-hydroxy-2-pentenal and a 5' phosphate group. Through its 3'-diesterase activity, APE1 then removes the 3' residue and Pol beta then synthesizes new DNA using the undamaged strand as a template. DNA ligase III ultimately seals the nick to complete the repair (40, 89). In both cases, BER repair proteins form complexes with a variety of accessory proteins whose function is critical to optimal repair. Many BER accessory proteins (e.g. BRCA, PARP, XRCC1, PCNA, RCF and XPG) also function in other cellular processes such as normal DNA replication (40, 89, 90).

3.2. Clinical implications of BER dysfunction

Inactivating mutations in BER glycosylases or BER accessory proteins can cause pathology (17, 93). BER protein variants that cause defects in the repair pathway, for example, have been seen in cell extracts from patients with head and neck cancer and in smokers with lung cancer and mutations in the DNA glycosylase MBD4 are implicated in the formation of colorectal, pancreatic and endometrial tumors (94). Polymorphisms and decreased activity of the glycosylase OGG1 may increase risk of lung cancer and MYH glycosylase dysfunction is associated with adenomatous colorectal polyposis and colorectal carcinoma. Pol beta and XRCC1 polymorphisms have been noted in a wide variety of tumors and are associated with cancer risk (40). MAP (MutYH-associated polyposis) is a recently described autosomal recessive colorectal adenoma and carcinoma predisposition syndrome associated with biallelic-inherited mutations of the human MutY homologue gene, MutYH. Colorectal tumors from MAP patients often exhibit mutational signatures of guanine-to-thymine transversions in the adenomatous polyposis coli (APC) and K-Ras genes, suggesting an important role for MutYH in the base excision repair of adenines mispaired with 7,8-dihydro-8-oxoguanine, a common lesion caused by oxidative damage to DNA (95-97). Individuals with MAP display a 50-60% chance of colorectal cancer at time of diagnosis which increases to approximately 100% by 65 years of age (97, 98).

3.3. Nucleotide Excision Repair (NER)

The NER pathway (Figure 4) evolved to cope with a variety of base alterations produced by exposure to environmental toxins, radiation and oxidative free radicals (39). Unlike BER where repair is initiated by specific N-glycosylases that recognize a single base alteration (e.g. uracil) or a small collection of similarly damaged bases, NER has a much broader substrate specificity (99). NER corrects many types of DNA damage that cause abnormal three-dimensional structure in the double helix and is especially critical for the repair of photolesions such as cyclobutane pyrimidine dimers. NER also corrects bulky DNA adducts formed by environmental and chemotherapeutic agents (e.g. cisplatin, aromatic hydrocarbons and arylamines) (100-102). The NER pathway involves the following basic steps:

1. Recognition of damage and recruitment of a multi-protein repair complex to the damaged site.
2. Nicking the damaged strand several nucleotides away on each side of the damaged base(s) and excision of the damaged region between the two nicks.
3. Filling in the resultant gap by a DNA polymerase using the non-damaged strand as a template and ligating the final nick to seal the strand.

Historically, NER has been described as being divided into two separate pathways- transcription-coupled repair (TCR) and global genome repair (GGR) based on whether the repair is triggered in transcriptionally active areas of the genome and activated by transcription enzymes or whether the repair occurs in transcriptionally silent sites. Recently, this designation is being challenged since there is no evidence that any other pathway other than NER is coupled to transcription-induced damage recognition and repair. Thus, it has been suggested to coin the terms NER and TC-NER for GGR and TCR respectively, as they likely represent the same repair pathways differing only at the damage recognition step (8). In either case, NER recognizes highly distorted DNA, sensing both helical distortions that affect Watson-Crick base pairing as well as chemical modifications to DNA (14, 103). NER can begin through damage recognition in any area of the genome (active or silent) by a heterodimeric damage-recognition complex composed of the XPC and HR23B proteins (39).

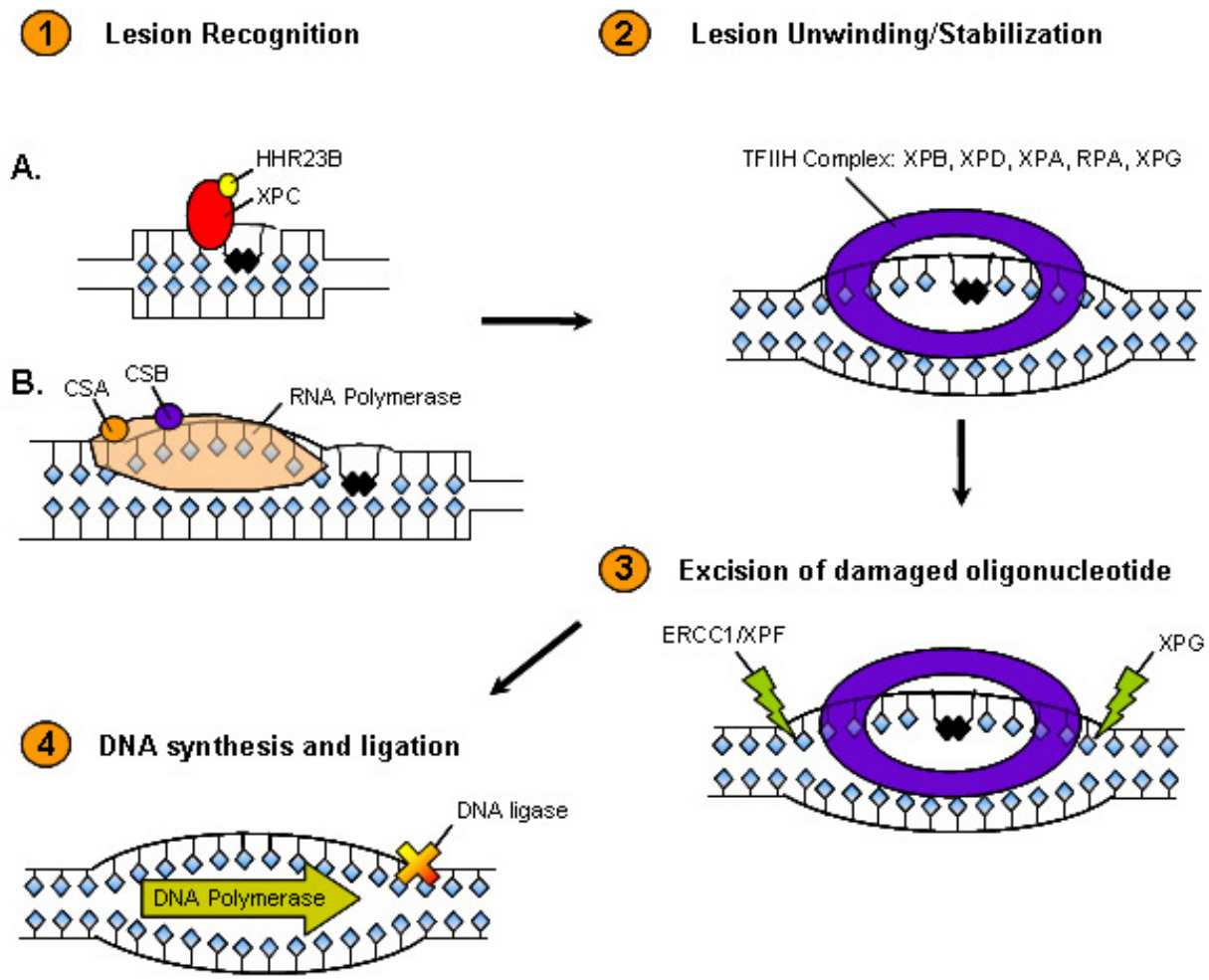

Figure 4. Nucleotide Excision Repair (NER). DNA lesions that distort the three-dimensional structure of the double helix trigger NER. Step 1: Lesion recognition: molecular sensing of damage (in this case, a cyclobutane dimer as represented by attached black diamonds) can occur by either the XPC-hHR23B heterodimer which scans the genome for DNA helix-distorting lesions (panel A) or by stalling of RNA polymerases and involvement of CSA and CSB (panel B). Step 2: lesion unwinding/stabilization: the TFIIH complex (containing the XPB and XPD repair helicases along with the XPA and RPA stabilizing proteins and the XPG endonuclease) is recruited. The XPB and XPD helicases of the TFIIH complex open the DNA helix around the lesion, and XPA and RPA stabilize and orient the unwound strands for excision. Step 3: removal of the damage: ERCC1/XPF and XPG makes the 5' and 3' incisions respectively, and the lesion-containing oligonucleotide is released. Step 4: synthesis and ligation: DNA polymerase fills in the gap using the undamaged opposing strand, and DNA ligase seals the strand.

The XPC-HR23B protein complex initially recognizes DNA damage and promotes local unwinding of DNA and recruitment of other NER proteins to the damaged area (102). DDB1 and DDB2 (XPE) may also assist in the recognition of UV photoproducts. The XPC/HR23B dimer recognizes DNA damage based on the extent of helical distortion of the DNA and binds to the damaged area of the DNA, further distorting the double helix and recruiting subsequent NER proteins to the damaged area (101). Alternatively, damage in transcribed strands of expressed genes may begin with stalling of RNA polymerase complexes (104, 105). In this manner, hindered RNA polymerase triggers initiation of NER and recruits the proteins CSA and CSB (defective in Cockayne's syndrome) to remove the stalled polymerase and facilitate entry of NER proteins (106).

After the initial damage recognition step, the general transcription factor TFIIH (which consists of ten subunits, including XPB and XPD) is recruited to the damage. XPB and XPD function as helicases (with 3' to 5' and 5' to 3' activity respectively) to unwind a stretch of 20-30 nucleotides that include the damaged site to relax the double helix and permit entry of successive proteins in the NER pathway (107). Subsequently, a complex forms consisting of RPA, XPA and XPG (108). XPA and RPA are thought to act as lesion verification proteins as well as scaffolding proteins (102). XPA binds to and stabilizes the open complex, and the RPA heterotrimer binds to and protects the separated strands in the unwound and damaged areas (109). Next, the damaged strand is cleaved via the participation of XPF-ERCC1 heterodimer and XPG junction-specific endonucleases that recognizes the

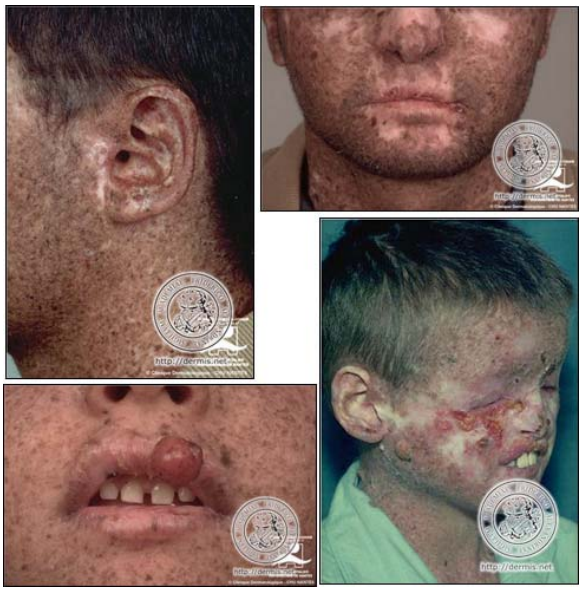

Figure 5. Clinical images of Xeroderma pigmentosum (XP), a defect in nucleotide excision repair (NER). XP is a rare disease characterized by photosensitivity, photodamage, cutaneous malignancies, severe ophthalmologic abnormalities and frequently early death from cancer. Shown are representative images of children and young adults affected by XP (courtesy of Diepgen TL, Yihune G et. al. Dermatology Online Atlas, published online at: http://www.dermis.net/doia/, copyrights reserved). Note the areas of hypo- and hyper-pigmentation, atrophy, scarring and pre-malignancy. Skin of affected patients is normal at birth but demonstrates striking pathology in UV-exposed areas (face, arms, hands) beginning in toddler-hood. Earliest signs of disease include irregular freckling, dryness and peeling. Over time, UV-exposed skin becomes erythematous, with telangiectasias, solar elastoses, lentigines, atrophy and scarring. Pre-malignant and malignant skin lesions such as basal cell carcinoma, squamous cell carcinoma and melanoma often first appear in childhood. The average age of developing skin cancer is 8 years old for XP patients, roughly 50 years sooner than the general public, and many patients die of malignancy in early adulthood. XP patients are at risk of non-UV malignancies as well, underscoring the role of NER in correcting both UV-dependent and UV-independent DNA damage.

junction between the single and double-stranded DNA created by the helicases (110). XPG nicks the DNA on the 3' side 2-8 nucleotides away from the lesion and ERCC1/XPF cuts the DNA on the 5' side 15-24 nucleotides away from the damage (111-114). After these two incisions are made a damage-containing oligonucleotide of 20-30 nucleotides in length is displaced along with the TFIIH-XPA-XPG-XPF/ERCC1 complex. The resulting gap is filled in by RFC, PCNA, DNA polymerase delta or epsilon using the opposite undamaged strand as a template with DNA ligase sealing the final nick (100-102, 115, 116).

3.4. Clinical consequences of defective NER: Xeroderma Pigmentosum

There are four known human diseases associated with defects in the NER pathway: Xeroderma pigmentosum (XP), trichothiodystrophy (TTD), Cockayne syndrome (CS) and Xeroderma pigmentosum-Cockayne syndrome (XP-CS) (115). Each is autosomal recessive and each is associated with enhanced UV photosensitivity as well as other symptoms (such as neurologic dysfunction) depending on the genetic defect (106). XP is comparatively more common than the other diseases, therefore we will focus our discussion of the clinical consequences of defective NER on this condition. XP is characterized by extreme photosensitivity and a high (> 1,000-fold) incidence of all types of skin cancer including malignant melanoma (117). The estimated frequency of XP is approximately 1:250,000 in North American populations but it is higher in other populations (1:100,000 or higher in Japan) (118). Persons affected by XP usually have a life expectancy into early adulthood, succumbing to cancer by 20-40 years of age. The underlying molecular defect of XP is defective NER caused by homozygous deficiency of any one of eight XP genes: XPA, XPB, XPC, XPD, XPE, XPF, XPG and XPV (119). The frequency of defects in each gene varies between different populations, but XPA deficiency is the most common genetic cause of XP (120).

Homozygotes for any one XP gene have severe UV-sensitivity that is caused by cumulative damage to sun-exposed areas of the body (especially the skin and eyes). Beginning in the first or second year of life, the skin rapidly begins to demonstrate signs of damage normally associated with *years* of sun exposure: hypo- or hyper-pigmented patchy macules, actinic keratoses, telangiectasias, atrophy, scarring and development of basal cell carcinomas, squamous cell carcinomas and melanomas (118) (Figure 5). Ocular problems including conjunctivitis, corneal clouding, visual loss and neoplasms also occur at a much younger age than unaffected controls. In addition, XP patients with defects specifically in XPA, XPB, XPD and XPG often manifest some degree of neurologic disease such as mental retardation, sensorineural deafness or abnormal motor function and progressive motor degeneration (121, 122). Nonetheless, neoplasia is the most sinister consequence of XP, and the overall cancer incidence for pediatric XP patients alone is 2,000 times that of the general population (118). The age of onset of the first skin cancer is typically *fifty years* earlier in XP patients than in non-XP controls (123), with many patients developing their first skin cancers in the first decade of life (compared to 60 years in the general population). Beside skin cancer, XP patients suffer a 20-fold increased risk of other malignancies including lung cancer, gastric carcinoma and brain cancer, reflecting the importance of NER in the repair of damage produced by agents other than UV (115). Overall, roughly 70% of persons with XP die by forty years of age from cancer of one kind or another, but aside from cancer, the most morbidity of NER dysfunction comes from intense photosensitivity and skin damage from UV exposure. Currently there is no widely-available therapy for treating XP other than strict avoidance of sunlight and careful surveillance and local control of pre-malignant or

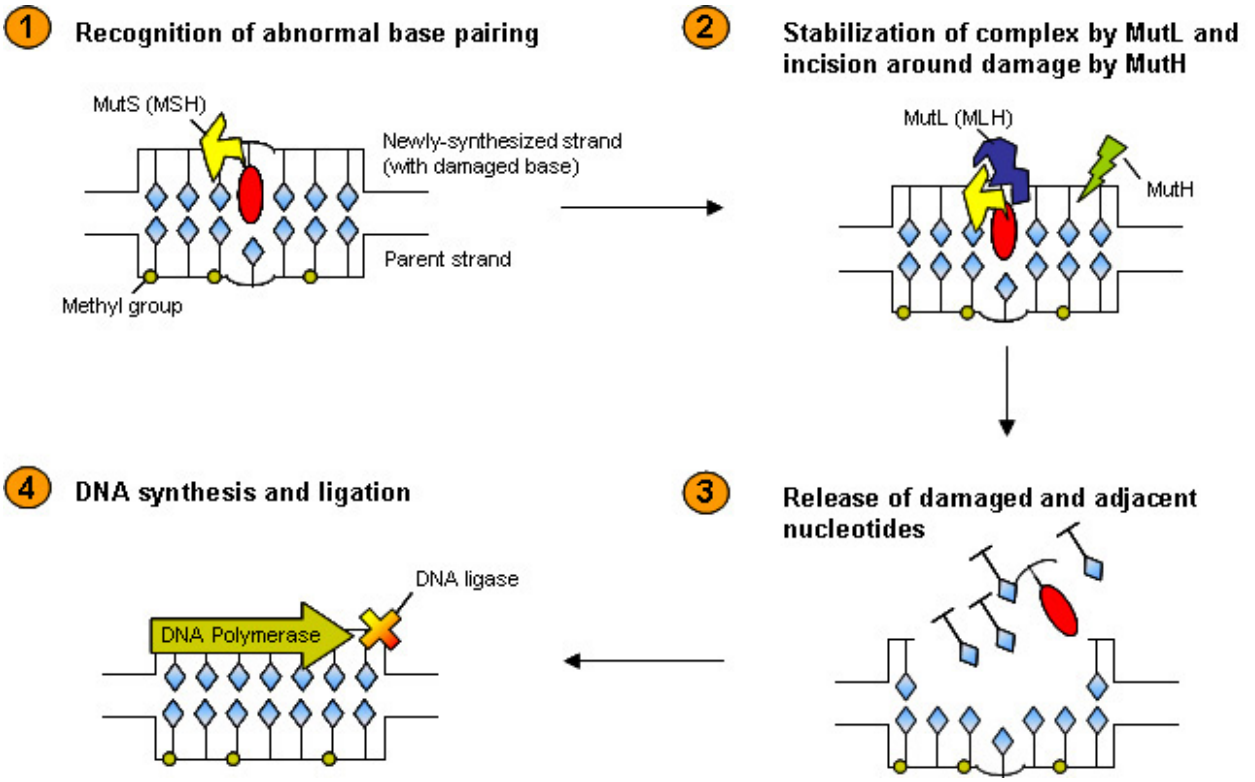

Figure 6. Mismatch Repair (MMR). MMR, like BER, corrects altered bases found in the genome, but is more widely applicable since the recognition step is not limited by the lesion-specific N-glycosylases of BER. Shown is a representation of prokaryotic mismatch repair, with mammalian homologues indicated in parentheses. Mismatch repair is initiated when MutS (or the mammalian homologue MSH) scans the genome and senses abnormal hydrogen bonding or altered three-dimensional conformation (step 1). In *E. coli*, differential methylation directs polarity of repair, whereas the process seems to be nick-directed in higher organisms. Next, MutL (MLH) stabilizes the complex and attracts helicases (step 2) and endonucleases to relax the damaged strand and cleave out the damaged oligonucleotide. MutH nicks at a single site (5' or 3' to the mismatch) and the damaged strand is degraded from that nick by exonucleases (step 3). DNA polymerase and DNA ligase fill in the correct sequence using the non-damaged strand as a template (step 4).

malignant lesions as they appear. The use of topical DNA repair enzymes (T4 endonuclease V) (124) and novel UV-protective strategies such as up-regulating cutaneous melanin levels for enhanced photoprotection (125) are being developed and hold promise for patients with NER dysfunction.

3.5. Mismatch Repair (MMR)

MMR is a highly-conserved repair pathway that corrects bases found to be mispaired outside usual Watson-Crick parameters (16, 42). In cases where the appropriate DNA N-glycosylase is available, damaged bases may be detected and corrected by the BER pathway, however MMR pathways have evolved to correct lesions that cause abnormal base pair bonding in the double helix but are not recognized by a BER glycosylase. Most often, mismatch occurs by replication infidelity, and the main function of MMR is almost exclusively to repair mismatches (or insertion-deletion errors) that occur during DNA replication (42). In MMR, determination of which base in the mispair to correct relies on differential identification of the newly-synthesized strand (presumed to have the "incorrect" base) which, at least in prokaryotes, probably is accomplished by recognition of differential methylation of the template and daughter strand (43). Since the basic mechanism of MMR is well-characterized in prokaryotes, and seems to be similar in eukaryotes (126, 127), we will feature the prokaryotic system in our description of MMR (Figure 6). In *E. coli,* MMR begins when MutS, the damage-sensing homodimeric protein, recognizes either true mismatches or insertions/deletions of up to four nucleotides in DNA. MutS then recruits the MutL homodimer to stabilize the complex and further recruit the MutH endonuclease. MutH incises/cleaves the newly synthesized strand and the MutS/MutL complex recruits the UvrD (Helicase II) protein to relax the double helix and unwind the strand from the nick (128). Next, single-strand exonucleases with specificity determined by the position of the nick relative to the mismatch excise the mismatch. ExoVII or RecJ is involved if the nick occurs 5' to the mismatch, whereas ExoI, ExoVII or ExoX function if the nick occurs 3' to the mismatch (129). In either case, excision of the incorrect nucleotide is followed by re-synthesis by DNA Polymerase III holoenzyme using the undamaged, methylated strand as a template and ultimately by ligation via DNA ligase activity (9, 16, 42, 130, 131).

Table 2. DNA repair deficient syndromes: clinical characteristics and molecular basis

Type of DNA Repair Defect	Associated Syndrome	Clinical Characteristics	Associated Gene(s)/OMIM #	Mode of Inheritance
Defective repair of double-strand breaks	Ataxia-telangiectasia	Progressive cerebellar ataxia, telangiectasias of skin and conjunctivae, oculomotor apraxia, frequent infections, choreoathetosis, immunodeficiency, increased risk for cancer (particularly leukemia and lymphoma)	*ATM*/607585 (mutations may cause loss of checkpoint regulation rather than RR dysfunction)	Autosomal recessive
	Nijmegen breakage syndrome	Short stature, progressive microcephaly with loss of cognitive skills, premature ovarian failure in females, recurrent sinopulmonary infections, increased risk for cancer (particularly lymphoma)	*NBS1*/602667	Autosomal recessive
	Bloom syndrome	Severe prenatal and postnatal growth retardation, sun-sensitive erythematous skin lesions mostly on the face, recurrent infections (otitis media and pneumonia), chronic pulmonary disease, learning disabilities, male infertility, premature ovarian failure in females, increased risk for cancer at an early age (epithelial, hematopoietic, lymphoid, connective tissue, germ cell, nervous system, and kidney)	*RECQ-Protein Like 3 (RECQL3/BLM)*/604610	Autosomal recessive
	Rothmund-Thompson syndrome	Facial rash in infancy that spreads and evolves into poikiloderma, sparse hair, sparse eyebrows/lashes, small stature, skeletal abnormalities (dysplasias, absent or malformed bones, osteopenia, and delayed bone formation), cataracts, increased risk for cancer (especially osteosarcoma)	*RECQ-Protein Like 4 (RECQL4)*/603780	Autosomal recessive
	Fanconi anemia	Bone marrow failure, physical abnormalities (short stature; abnormal skin pigmentation; malformations of the thumbs, forearms, skeletal system, eyes, kidneys and urinary tract, ear, heart, gastrointestinal system, oral cavity, and central nervous system; hearing loss; hypogonadism), developmental delay, and increased risk of malignancy (acute myeloid leukemia; solid tumors of the head and neck, skin, GI tract, and genital tract)	*FANCA*/607139 *FANCC*/227645 *BRCA2/FANCD1*/600185 *FANCD2*/227646 *FANCE*/600901 *FANCF*/603467 *XRCC9/FANCG*/602956 *FANCI*/609053 *FANCJ*/609054 *FANCL*/608111	Autosomal recessive
	Werner syndrome	Short stature, slender limbs, stocky trunk, beaked nose, scleroderma-like skin changes, hypogonadism, premature (starting in 20s or 30s) appearance of features associated with normal aging (loss and graying of hair, wizened facies, cataract, arteriosclerosis, diabetes mellitus; osteoporosis, myocardial infarction, cancer)	*RECQ Protein-Like 2 (RECQL2/WRN)*/604611 *Lamin A/C (LMNA)*[1]/150330	Autosomal recessive Autosomal dominant
Defective mismatch repair	Hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome	Increased risk of colorectal cancer (2/3 of cases in proximal colon, average age at diagnosis 44), as well as cancer of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract (transitional cell carcinoma), brain (glioblastoma), and skin (sebaceous neoplasm)	*MLH1*/120436 *MSH2*/609309 *MSH6*/600678 *PMS2*/600259	Autosomal dominant
Defective base excision repair	*MYH*-associated polyposis (MAP)	Attenuated or atypical colorectal adenomatous polyposis; increased risk of colorectal cancer	*MUTYH*/604933	Autosomal recessive[2]
Defective nucleotide excision repair	Xeroderma pigmentosum/ DeSanctis-Cacchione syndrome	Sun sensitivity, ocular involvement, and greater than 1000-fold increased risk of cutaneous and ocular neoplasms, 30% of affected individuals have neurologic manifestations, including acquired microcephaly, diminished or absent deep tendon stretch reflexes, progressive sensorineural hearing loss, and cognitive impairment	*XPA*/278700 *ERCC3/XPB*/133510 *XPC*/278720 *ERCC2/XPD*/126340 *DDB2/XPE*/600811 *ERCC4/XPF*/133520 *ERCC5/XPG*/133530 *POLH/XP-V*/603968	Autosomal recessive
	Photosensitivive trichothiodystrophy (TTDP)	Photosensitivity (although no significant increase in skin cancer), erythroderma, brittle hair and nails, ichthyotic skin, physical and mental retardation, low birth weight, short stature, lack of subcutaneous fatty tissue, hypogammaglobulinemia, recurrent infections, absent breast tissue, hypogonadism, aged appearance, cataract, no significant increase in skin cancer	*ERCC2/XPD*/126340 *ERCC3/XPB*/133510 *TFB5 (tenth subunit of transcription factor IIH)*/608780	Autosomal recessive
	Cockayne syndrome	'Cachectic dwarfism' (abnormal and slow growth and development), cutaneous photosensitivity (although no significant increase in skin cancer), thin, dry hair, a progeroid appearance, progressive pigmentary retinopathy, sensorineural hearing loss, dental caries, disproportionately long limbs with large hands and feet, and flexion contractures of joints (knee contractures result in characteristic 'horseriding stance'), delayed neural development and severe progressive neurologic degeneration resulting in mental retardation	*ERCC8 (CS TypeA)*/609412 *ERCC6 (CS TypeB)*/609413	Autosomal recessive
Defects in multiple DNA repair and damage-response pathways	Li-Fraumeni syndrome (LFS)	Individuals with LFS are at increased risk for developing multiple primary cancers, particularly soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma, as well as cancer of the colon, pancreas, adrenal cortex, and brain	*TP53*/191170 *CHEK2*/604373	Autosomal dominant
	Hereditary breast-ovarian cancer syndrome	Increased risk of breast cancer (2/3 of cases diagnosed before age 50) and ovarian cancer; mutations in *BRCA1* are also associated with increased risk of prostate cancer in males; mutations in *BRCA2* also associated with increased risk of breast cancer in males, and may be associated with increased risk of melanoma and pancreatic cancer	*BRCA1*/113705 *BRCA2*/600185	Autosomal dominant

[1]Heterozygous missense mutations in *LMNA* have been identified in individuals with 'atypical Werner syndrome'. Atypical Werner syndrome has an earlier age of onset (early 20s) and faster rate of progression than classic Werner syndrome [2]Family history of colorectal cancer has suggested vertical transmission in a significant number of families, although biallelic mutations have been found in two generations in some of these families

In contrast to prokaryotic MMR, eukaryotic MMR probably does not use differential methylation of DNA strands for strand discrimination. Instead, data suggest that eukaryotic MMR pathways may use single-strand nicks that arise in replication (the 5' or 3' termini of Okazaki fragments in the lagging strand or the 3' terminus of the leading strand) as a signal for strand specificity to direct MMR (43). The eukaryotic homologues of MutS and MutL- MSH and MLH respectively- function as heterodimers to sense damage and initiate MMR (9). MutS alpha (MSH2/MSH6) and MutS beta (MSH2/MSH3) are major mismatch recognition proteins in eukaryotes. The MutS alpha complex recognizes and repairs both base-base mismatches and insertion-deletion mismatches whereas the MutS beta complex is primarily involved in the repair of insertion-deletion mismatches. Eukaryotic MutL homologues make up three MutL heterodimers, MutL alpha (MLH1/PMS2), MutL beta (MLH1/PMS1), and MutL gamma (MLH1/MLH3). Whereas the roles of MutL beta and MutL gamma remain to be characterized, MutL alpha

participates in both the MutS alpha- and MutS beta-involved MMR (130). Eukaryotic homologues of MutH or DNA helicase II/UvrD have not yet been identified (9, 16, 42, 43). Eukaryotic MMR, initiated when MutS alpha or MutS beta binds to the mismatch, may involve biochemical association with proliferating cell nuclear antigen (PCNA) to evoke other MMR proteins such as replication factor C (RFC), the high-mobility group box 1 (HMGB1), and replication protein A (RPA) to the process (9, 16, 42, 43, 132). Overall, eukaryotic MMR is similar to prokaryotic MMR in that excision of the lesion by exonuclease activity is followed by re-synthesis of DNA by polymerases and ultimately by ligation by DNA ligase (42). Recently, the MMR system has been reconstituted *in vitro* using purified human proteins (MutS alpha or MutS beta, MutL alpha, RPA, EXO1, HMGB1, PCNA, RFC, polymerase delta, and ligase I) (130).

3.6. Clinical Consequences of Defective MMR

In humans, inactivation of the MMR system predisposes individuals to gastrointestinal and uterine cancers (2, 133, 134). Lynch syndrome is an autosomal dominant, highly penetrant condition characterized in part by defective MMR wherein hereditary nonpolyposis colorectal cancer (HNPCC) occurs with high frequency (135, 136). HNPCC is caused by mutations of various MMR proteins, with defects in *MLH1, MSH2, MSH6,* and *PMS2* all being described (5, 137). Most cases involve either MSH2 or MLH1, genes that are essential for formation of MutS/MutL homologous heterodimers that function in normal cell division. Just under two thirds of cases of HNPCC are associated with MLH1 defects with another third of cases being caused by MSH2 defects. Patients with this disorder suffer an increased risk of colorectal cancer at a young age (average age at diagnosis 44) and are at risk for carcinomas of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract (transitional cell carcinoma), brain (glioblastoma), and skin (sebaceous neoplasm). A critical role for MMR in preventing colorectal cancer is further evidenced by non-HNPCC cases of colon cancer. These tumors exhibit microsatellite instability (variations in the number of repeat units of short tandemly repeated sequences thought to be a consequence of defective DNA repair) and are often associated with methylation and silencing of the MLH1 gene (138, 139). Chan and colleagues recently described a familial cancer syndrome of colorectal and endometrial carcinomas caused by differential methylation patterns of the *MSH2* gene, raising the possibility that epigenetic mechanisms affecting MMR may predispose to malignancy (140).

3.7. Recombinational Repair (RR)

A double-stranded break is one of the most severe form of DNA damage that a cell can suffer in which both strands of the double helix are broken on the sugar phosphate backbone in relatively close proximity to each other (86, 141). Double-stranded breaks may be caused by exogenous insults (e.g. ionizing radiation, chemotherapy) or endogenous sources of damage (reactive oxygen species, replication errors) and clearly lead to genomic instability, apoptosis and/or mutation via insertions, deletions, translocations and aneuploidy (142-144) . The cell uses RR to correct not only double-strand breaks but also damage caused by interstrand crosslinks and other circumstances brought on by collapse or blockage of replication forks (12, 145-147). Double-stranded breaks are repaired by RR through either of two highly evolutionarily conserved pathways: homologous recombination (HR) and non-homologous end joining (NHEJ) (144). HR is mediated by a template with high sequence homology (usually from the sister chromatid) and is fairly accurate. In contrast, NHEJ does not involve a homologous template, and is therefore much more error-prone (141). In both HR and NHEJ, double-stranded breaks are recognized by a protein complex known as MRN which consists of three subunits Mre11, Nbs1 and Rad50. This damage recognition complex is thought to then activate the ataxia telangiectasia mutated kinase (ATM) protein (148) which transduces the damage signal through a cascade of downstream effector kinases. While not a formal recombinational repair enzyme itself, ATM may halt replicative processes so that the double-stranded break may be repaired (149). HR acts in coordination with S and G2 cell cycle checkpoint signals to eliminate chromosomal breaks before cell division occurs, although direct molecular interactions between checkpoint response and RR proteins have not been firmly established (150).

HR is thought to involve the following steps: (1) damage recognition, (2) nuclease activity, (3) Rad51 (with accessory proteins) that binds single-stranded DNA and invades the sister to form a D-loop, (4) DNA synthesis and ligation using the sister as a template, and (5) release the borrowed sister chromatid DNA. HR can lead to two DNA products: (1) a non-crossover event in which there is only a small portion of heteroduplex DNA flanked by the original parent sequence, or (2) a crossover event in which the area that was cleaved is now flanked by completely new genetic sequence. In either case, since the homologous sister chromatid was central to repair of the lesion, fidelity of the process is relatively maintained (151). HR involves the cooperative effort of several important proteins including RAD51 and its paralogs, RAD52, RAD54, and RPA and may also involve the MRN complex and RecQ helicases (86).

In NHEJ, the sister chromatid is uninvolved in repair and fidelity is sacrificed to prevent further damage that might occur to nascent unprotected DNA ends after strand breakage. As a result, the resultant repaired DNA product after NHEJ is much more likely to exhibit altered nucleotide sequence than either before strand breakage or if the damage had been corrected by HR (143). As in HR, the process begins with damage recognition, but then the pathways differ. In NHEJ, a heterodimeric protein (Ku70/80) binds to free ends in the break to protect the DNA from further damage and to recruit subsequent proteins. A DNA-dependent protein kinase is recruited to the damage and connects the free ends of the DNA together while nucleases such as WRN, FEN-1 and Artemis remove overhanging ends to promote end joining (152). Gaps are filled in by X family polymerases (lambda or mu) and nicks are sealed by DNA ligase IV and the accessory protein XRCC4 (86, 153).

3.8. Clinical consequences of defective RR

Clinically-described syndromes whose molecular pathogenesis may involve faulty RR include various premature aging and/or malignancy-prone syndromes such as Werner syndrome, ataxia telangiectasia (AT), Bloom syndrome, Nijmegen breakage syndrome (NBS), and the Rothmund-Thomson syndrome (86, 154, 155). Fanconi anemia (FA) is a rare autosomal recessive disease that is characterized by congenital abnormalities, progressive bone marrow failure and cancer susceptibility. FA patients exhibit heightened sensitivity to pharmacologic and radiation agents that cause strand breakage, presumably because of defective RR. A molecular connection between FA and breast cancer was established when the FancD1 gene was identified as BRCA2 (156). In fact, the FA-associated gene products along with BRCA1 and BRCA2 function in a common pathway that regulates cellular responses to DNA damage by interacting with a host of checkpoint response (e.g. ATM) and DNA repair proteins (RAD51) (157, 158). In 1994, the breast cancer susceptibility gene *BRCA2* was identified on chromosome 13 (159). Deficiency of BRCA2 results in genomic instability and cancer predisposition (160) possibly due to failure to repair DNA double-strand breaks through HR (161, 162). BRCA2 regulates HR by facilitating hRad51 binding to ssDNA (163, 164). Inherited mutation in one allele of BRCA2 results in increased susceptibility to both breast and ovarian cancer, while inheritance of some bi-allelic mutations of BRCA2 causes a constellation of symptoms similar to FA (165).

4. SUMMARY

Inherited or acquired flaws in DNA damage-sensing and/or DNA repair gene function lead to characteristic pathophysiology with the specific constellation of symptoms depending on which repair pathway(s) are affected by gene inactivation (Table 2). Much has been learned regarding the importance of various repair pathways in genome maintenance after various genotoxic insults (e.g. the importance of NER in correcting UV-mediated DNA damage or the central role of RR in restoring proper chromosome structure after strand breakage). Studying rare individuals with familial cancer predisposition syndromes due to inheritance of loss-of-function mutations in DNA repair genes has led to profound understanding of the molecular pathophysiology underlying very common illnesses such as sporadic cancer in the general population. Clearly many of the same genes that underlie familial cancer predisposition syndromes are also frequently mutated in cancers in the general population. It is likely that polymorphisms or epigenetic factors that subtly affect protein function or intracellular concentration of the very same proteins play a large role in sporadic cases of diseases such as cancer and other age-related processes (100, 166-169). Further investigation into DNA damage and repair pathways and especially their role in normal aging and sporadic malignancy holds the promise of understanding basic molecular mechanisms of common human disease and introduces the concept of disease prevention by manipulation of repair pathways.

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Abbreviations: NER: nucleotide excision repair, BER: base excision repair, MMR: mismatch repair, RR: recombinational repair, ATM: ataxia-telangiectasia mutated, ATR: ATM-Rad3-related, LFS: Li-Fraumeni syndrome, 8-oxoG: 8-oxo-7,8-dihydroguanine, NHEJ: non-homologous end joining, AP: apurinic/apyrimidinic, MAP: MutYH-associated polyposis, TCR: transcription-coupled repair, GGR: global genome repair, XP: Xeroderma pigmentosum, TTD: Trichothiodystrophy, CS: Cockayne syndrome, XP-CS: xeroderma pigmentosum-Cockayne syndrome, HNPCC: hereditary nonpolyposis colorectal cancer, HH: homologous recombination, FA: Fanconi anemia

Key Words: DNA repair, Nucleotide Excision Repair, Base Excision Repair, Mismatch Repair, Recombinational Repair, MutYH-associated poluposis, Xerderma Pigmentosum, Hereditary Nonpolyposis Colorectal Cancer, Fanconi anemia, Review

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