Chapter 27

Cancer and Genomic Instability

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1. INTRODUCTION

Cancer is a complex disease that is often associated with genomic instability. Since 1975 when an important role of genomic (chromosome) instability was first postulated in the development of lymphoid malignancies [1], it has been recognized as a key hallmark of cancer due to its characteristics in most human cancers [2]. In 2000s, many new findings have highlighted that certain DNA-repair pathways and cell cycle–control processes have important consequences for genomic stability and cancer cell biology. The deficiency of DNA-repair pathways may therefore result in genomic instability and cancer development.

2. DNA-REPAIR PATHWAYS

A large body of evidence has demonstrated that the genomic DNA of eukaryotic cells is constantly challenged by genotoxic stresses arising from either physiological metabolism or environmental exposure or both which frequently result in numerous DNA lesions (Table 27.1). It is estimated that every day thousands of DNA lesions are induced in each human cell [3]. However, multiple important DNA-repair pathways, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), nonhomologous end joining (NHEJ), and homology-directed repair (HDR) pathways, have evolved to remove the damaged regions from genomic DNA, thus preventing a key molecule from the deleterious consequences of lesion accumulation.

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TABLE 27.1 DNA Lesions and Repair Pathways

DNA-Damage Source	Type of Lesion	DNA-Repair Pathway
ROS, IR, alkylating agents	Altered base, abasic site, SSBs	BER
Ultraviolet light, cisplatin intrastrand adducts, polyaromatic hydrocarbons	Intrastrand cross-links, bulky DNA adducts	NER
IR, alkylating agents, cisplatin	Interstrand cross-links, DSBs	DSB repair (NHEJ/HR)
Replication errors	Base mismatches, insertions and deletions	Mismatch repair

This table was drawn based on that summarized elsewhere Reed SH, et al. Nucleotide excision repair in chromatin: damage removal at the drop of a HAT. DNA Repair 2011;10(7):734–42.

2.1 Base Excision–Repair Pathway

It has been indicated that small, nonhelix-distorting base lesions induced by oxidization, alkylation, and deamination in genomic DNA are the primary target of the BER pathway [4,5]. Generally, the BER process can be divided into four basic steps: apurinic/apyrimidinic (AP) site formation and excision, DNA end processing, gap filling, and DNA ligation (Fig. 27.1) [5]. It is believed that the BER pathway is initiated by DNA glycosylase that binds and removes the damaged bases, forming an abasic site–containing intermediate [4,5]. The apurinic endonuclease 1 (APE1) has the AP endonuclease activity and cleaves at the 5′-side of the AP-site ribose, producing either a 5′-deoxyribose phosphate (dRP) causing nonoxidized damages or a 5′-ribose phosphate causing oxidized damages. This process generates a temporary DNA single-strand break (SSB)—one of the most frequent lesions in genomic DNA. The 5′-dRP intermediate is further processed by DNA polymerase β (Polβ) which possesses the 5′-deoxyribose phosphate (dRP) lyase activity removing the 5′-dRP and forming a single-nucleotide gap that can be filled up by DNA Polβ. Other proteins, such as APE1, polynucleotide kinase 3′-phosphotase (PNKP), aprataxin (APTX), and the X-ray-repair cross-complementing protein 1 (XRCC1), may also be involved in the repair of the damaged termini. The nicked DNA is then ligated by DNA ligase 3 (LIG3). This pathway is termed short-patch (1 nt) BER. However, the SSBs induced by the oxidized ribose phosphate can be repaired through the long-patch BER pathway. Poly(ADP-ribose) polymerase 1 (PARP1), a chromatin-associated enzyme that catalyzes protein ADP-ribosylation and functions as an SSB sensor, primarily binds and is rapidly activated by DNA strand breaks. As a result, DNA end-processing enzymes, such as APE1, PNKP, APTX, and PARP1, get modified with branched poly(ADP-ribose) chains that repair the damaged 3′-termini. Simultaneously, flap endonuclease 1 (FEN1) that is activated by proliferating-cell nuclear antigen (PCNA) and PARP1 remove the damaged 5′-terminus of two or more nucleotides (2–12 nt). The left gap is then filled up with Polβ and Polδ/ε, and the nicked DNA is rejoined by DNA ligase 1 (LIG1) (Fig. 27.1).

2.2 Nucleotide Excision–Repair Pathway

NER is the major pathway for removing bulky, conformation-distorting DNA lesions induced by exogenous genotoxic agents such as UV irradiation, environmental mutagens, and certain chemotherapeutic drugs [6,7]. As it is demonstrated, two NER sub-pathways contribute to the removal of these DNA lesions. The global genome NER (GG-NER or GGR) has evolved to repair the lesions throughout the whole genome, while transcription-coupled NER (TC-NER or TCR) specifically removes DNA lesions in the transcribed strand of the activated genes.

Upon UV-induced DNA damage, GG-NER is triggered by the UV-damaged DNA-binding protein (UV-DDB) and XPC/RAD23B/CETN2 complexes that recognize and bind UV-induced DNA photolesions such as cyclobutane pyrimidine dimers (CPD) and 6–4 photoproducts (6–4 PP) (Fig. 27.2 left). Once the XPC complex is bound to the lesion, the component RAD23B dissociates from the complex. On the other hand, TC-NER is initiated by the stalled RNA polymerase II (RNA PolII) during transcription elongation (Fig. 27.2 right). It has been demonstrated that RNA PolII arrested by DNA damage interacts closely with the Cockayne syndrome B protein (CSB), the UV-stimulated scaffold protein A (UVSSA), and the ubiquitin specific–processing protease 7 (USP7). Upon stalling at the lesion site, the Cockayne syndrome WD repeat protein CSA and CSB complex is formed and causes RNA PolII to move backwards (also termed backtracking), which makes the lesion accessible for repair. After lesion recognition, the transcription initiation factor IIH (TFIIH) complex in which XPB, XPD, and other five subunits form a core complex and the single-strand DNA-binding protein RPA (the replication protein A) are recruited to the lesion site, hence they form the pre-incision complex in both the GG-NER and TC-NER pathways. XPB and XPD may help create transcription bubble because of their helicase and ATPase activities.

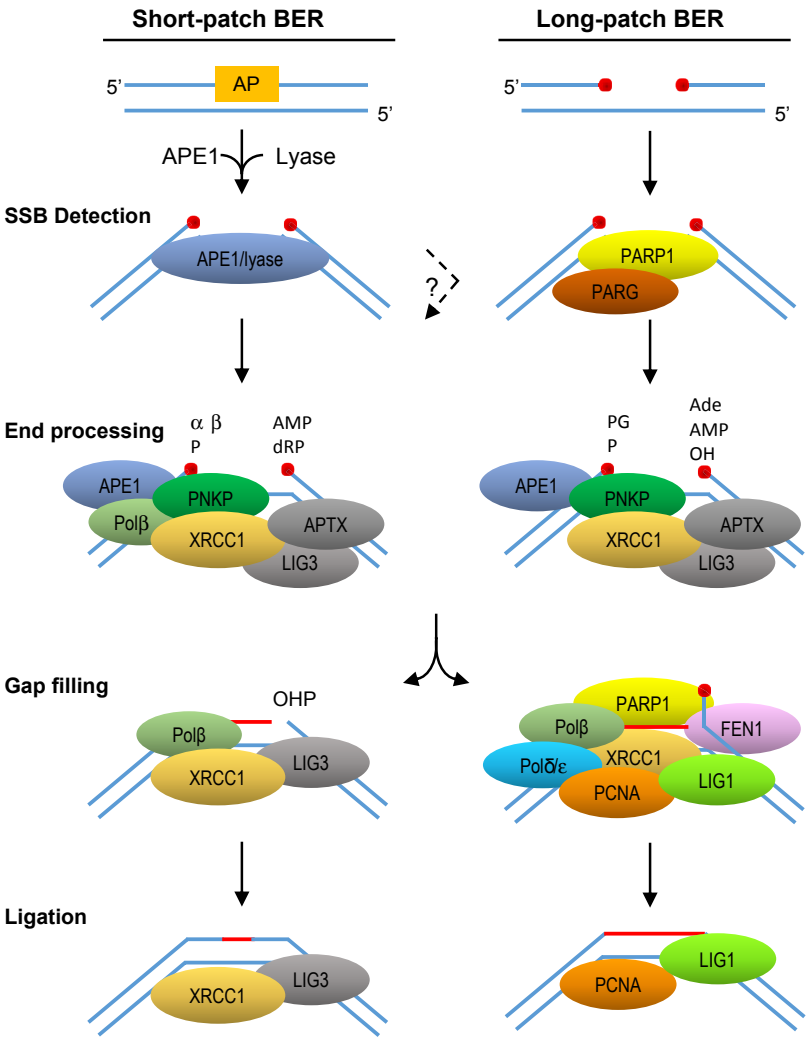

FIGURE 27.1 A model for the base excision-repair pathway. Single-strand breaks arisen indirectly from enzymatic incision at the AP site during BER or directly from disintegration of oxidized deoxyribose are primarily removed via the BER pathway which is generally divided into short-patch and long-patch BERs based on the size of nucleotide patch length. Numerous proteins overlap in the "four-step" repair processes. *Red circles* indicate damaged termini. This model was redrawn according to that proposed by Caldecott [5]. *We thank Nature Publishing Group's for permission, http://www.nature.com/nrg/journal/v9/n8/full/nrg2380.html.*

The XPG endonuclease also binds to the pre-incision NER complex. After dissociation with the CAK (CDK-activating kinase) subcomplex, the helicase activity of the TFIIH complex further unwinds the double helix, thus facilitating XPA to recruit and activate XPF/ERCC1. Once the 5′-side of the lesion was incised by the XPF/ERCC1 heterodimer, XPG is activated and incises the damaged strand at the 3′-side of the lesion releasing a 22–30 nt–long strand. PCNA then recruits DNA polymerase δ, κ, or ε to fill up the gap, and DNA ligase I or III rejoins the nick ends to complete the repair process.

2.3 Mismatch-Repair Pathway

Mismatch repair (MMR) is a major pathway that removes mismatch lesions generated during DNA replication, which represents a considerable threat to the genomic integrity [8,9]. The initiation of the MMR pathway can be attributed to the recognition of mismatches by either MutSα (MSH2–MSH6 heterodimer) or MutSβ (MSH2–MSH3 heterodimer) which recruits MutLα to form an ATP dependent–ternary complex (Fig. 27.3), thus facilitating this complex to undergo an ATP driven–conformational change and form a sliding clamp. This clamp can track the strand discontinuity in either direction along DNA. Replication factor C (RFC) acting as a clamp loader binds the 3′-terminus of the strand break and helps load PCNA onto the DNA. The clamps that slid to the upstream RFC loaded at the 5′-terminus of the strand break lead to RFC disassociation with DNA, facilitating the recruitment of EXO1 that mediates the degradation of the mismatch-containing

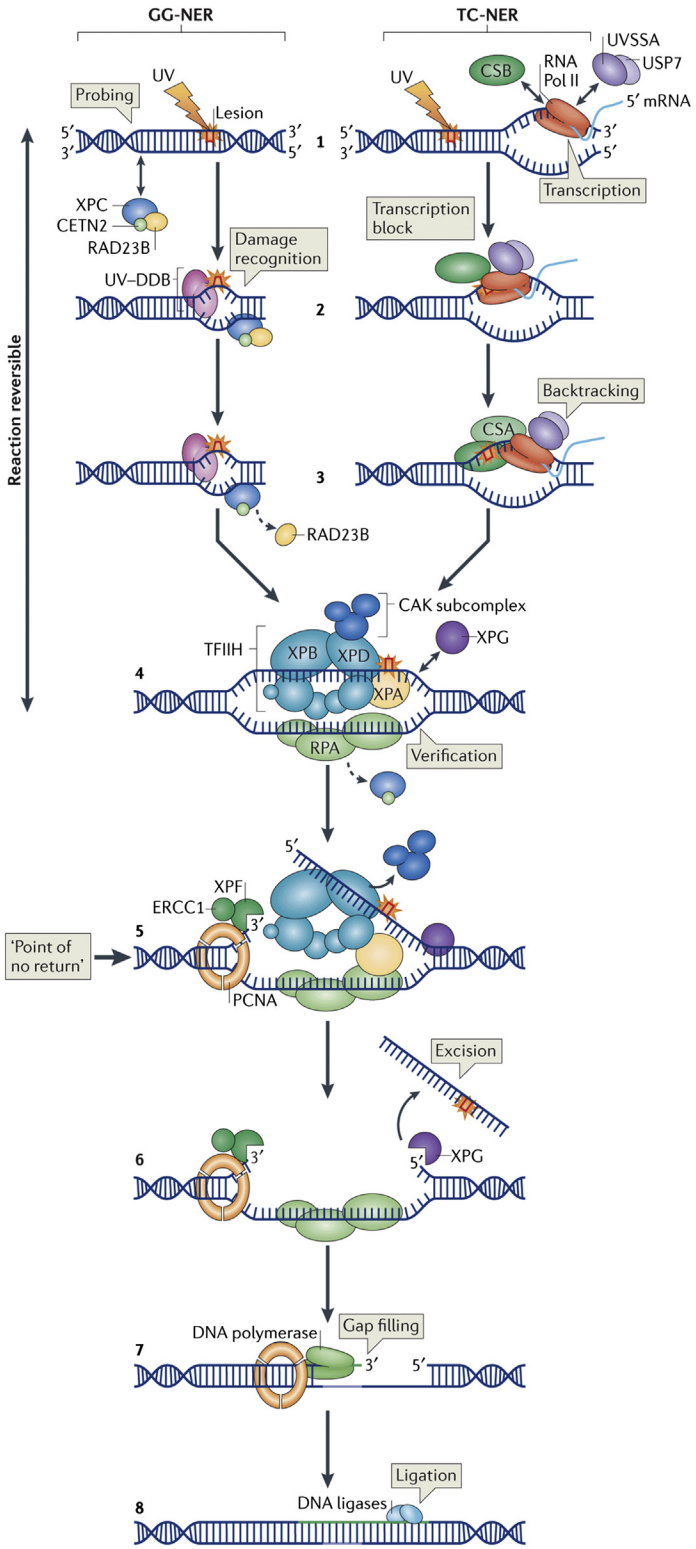

FIGURE 27.2 A model for the nucleotide excision–repair pathway. Bulky DNA lesions induced by exogenous genotoxic agents are mainly repaired by NER which is divided into global genome NER (GG-NER) and transcription-coupled NER (TC-NER) sub-pathways. *Adapted from Marteijn JA, et al. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol 2014;15(7):465–81. We thank Nature Publishing Group's for permission, http://www.nature.com/nrm/journal/v15/n7/full/nrm3822.html.*

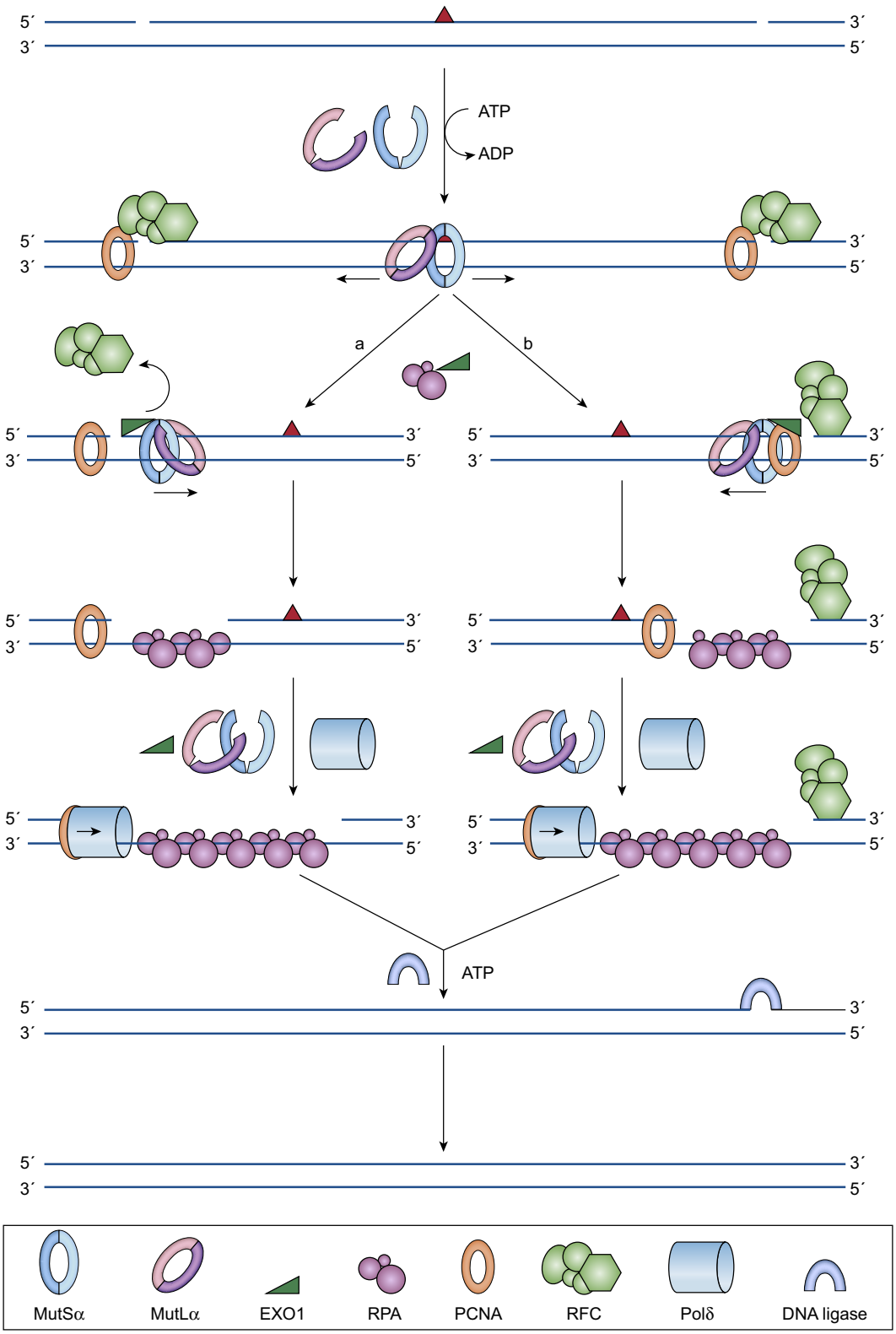

FIGURE 27.3 **A model for the mismatch-repair pathway.** Mismatch lesions arisen during DNA replication are predominantly removed via the mismatch-repair pathway. *Adapted from Jiricny J, et al. The multifaceted mismatch-repair system. Nat Rev Mol Cell Biol 2006;7(5):335–46. We thank Nature Publishing Group's for permission, http://www.nature.com/nrm/journal/v7/n5/full/nrm1907.html. Copyright © 2006 Nature Publishing Group.*

strand in a 5′→3′-direction (Fig. 27.3A). RPA then binds and stabilizes a single-strand gap. Once the mismatch lesion is removed, the EXO1 activity is suppressed by MutLα and released from the DNA. DNA Polδ then loads at the 3′-terminus of the discontinuity that is bound with PCNA homotrimer which is essential for Polδ-mediated DNA synthesis. This DNA Polδ resynthesizes a new DNA to fill the gap, and DNA ligase I seals the remaining nick. The clamps that track the downstream PCNA homotrimer bind at the 3′-terminus of the strand break (Fig. 27.3B) recruiting and/or activating EXO1 that triggers the degradation of the strand containing a mismatch in a 3′→5′-direction. After the removal of the mismatch lesion, Polδ is responsible to fill the gap, and DNA ligase I seals the remaining nick to complete the process of MMR.

2.4 Repair of DNA Double-Strand Breaks

Canonical nonhomologous end joining (C-NHEJ) and HDR are two major pathways engaged to repair DNA double-strand breaks (DSB). The initiation of C-NHEJ is triggered by heterodimer Ku (Ku70 and Ku80) that binds to the ends of DSB and recruits the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to form the DNA-PK holoenzyme [10]. The active kinase complex phosphorylates other repair-related proteins and promotes Artemis-mediated end processing. DNA integrity is then restored by rejoining of the DNA ends by the Lig4/XRCC4/XLF complex. C-NHEJ is a fast but error prone–repair machinery.

In contrast to C-NHEJ, homologous recombination HDR is an error-free DSB-repair pathway that is primarily governed by homologous sister chromatids in higher eukaryotes. HDR preferentially monitors the DSB that occurs in the late S and G2 phases of the cell cycle [11]. It is believed that the HDR-repair pathway is initiated by binding of ATM (the ataxia-telangiectasia-mutated gene) to the DSB [12] that recruits repair proteins such as BRCA1 (breast cancer 1 gene) and MRN complex (Mre11, Rad50, and Nbs1) to process the ends of DSB, thus generating a long 3′-single-stranded DNA (ssDNA) overhanging on both sides of the break [10]. RPA then binds and stabilizes ssDNAs. However, the binding of the recombinase RAD51 results in the release of RPA from DNA. RAD51 acts together with RAD54 to search for DNA homology, the ATPase activity of RAD54 helps unwind DNA facilitating strand invasion [13]. After displacement loop (D-loop) formation and strand invasion, a DNA polymerase extends the end of the invading 3′-strand by synthesizing a new DNA. After DNA synthesis, two sub-pathways—double-strand break repair (DSBR) and synthesis-dependent strand annealing (SDSA) may be engaged [10]. Both 3′-overhangs are involved in DSBR to generate a double Holliday junction which is then converted into recombination products by nicking endonucleases, resulting in crossover (common) or non-crossover products. In SDSA, only one 3′-overhang participates to form a single Holliday junction, resulting in non-crossover products.

3. GENOMIC INSTABILITY IN HEREDITARY CANCER

As suggested by the mutator phenotype hypothesis, tumors arise as a consequence of the accumulation of mutations and the corresponding dysregulation of key cellular functions [14]. However, the natural mutation rates in human cells are insufficient to account for the genomic instability observed in tumor cells. In addition, no more than 150 genes have been identified as cancer drivers [15], while most of the mutations observed in cancer cells do not present a significant functional impact on the neoplastic phenotype. Therefore, to confer oncogenic transformation, pre-neoplastic cells have to incur the increased rates of mutagenesis which will aggregate as a consequence of initial transformation and aggravate throughout the whole process of neoplastic progression.

The genomic maintenance involves the integration of multiple DNA damage–repair mechanisms to remove molecular lesions resulted from various intrinsic and extrinsic challenges. The identification of mutations in genes responsible for sensing and repairing DNA damages has provided a strong support for the mutator hypothesis. In contrast to somatic mutations which sporadically occur in individual cells, germline mutations may have been present since birth in every cell in an individual's body. Cells in individuals carrying germline mutations of genes that primarily function to maintain the genomic stability may present higher intrinsic mutagenesis rates due to haplodeficiency which makes precancerous cells more susceptible to genotoxic challenges. For example, the loss of the remaining wild-type allele will completely abrogate the gene function, thus resulting in uncontrolled mutation accumulation that will eventually trigger the neoplastic transformation, as predicted by the mutator hypothesis. Therefore, individuals with an inherent germline mutation of genes that encode DNA damage–response proteins frequently elicit a number of genomic instability syndromes, and these disorders often result in a heightened predisposition to cancer, as seen in familial cancer syndromes.

DNA-repair defects are a common cause of inherited cancer susceptibility, and many examples have now been recognized. Some of these are autosomal recessive conditions such as ataxia telangiectasia, Fanconi anemia (FA), and xeroderma pigmentosum (XP). Hereditary nonpolyposis colon cancer and breast cancer susceptibility due to mutations of MMR cluster *BRCA1/2*, respectively, are examples of autosomal dominant cancer susceptibility syndromes due to inherited alterations in genes that are involved in DNA MMR and HDR.

3.1 Li–Fraumeni Syndrome and TP53

The Li–Fraumeni syndrome (LFS) is an autosomal dominantly inherited disorder primarily determined by heterozygous germline mutations in the tumor-suppressor gene *TP53* (located at chromosome 17p13) [16]. *TP53* encodes a transcription factor activated in response to various stress signals, including DNA-damage signaling, and is thus implicated in the maintenance of genomic stability. The activation of TP53 prevents the proliferation of cells with damaged DNA by inducing cell-cycle arrest to allow DNA repair or directly trigger programmed cell death upon irreversible DNA damages. Because of its comprehensive role in DNA-damage response, TP53 is also defined as "the guardian of the genome." LFS individuals carry missense mutations of *TP53*, most frequently within exons 5–8 coding for the DNA-binding domain of the protein. Such mutation nullifies the TP53 transcriptional activity resulting in haploinsufficiency with reduced protein expression and consequently impairs the genomic protective role of TP53. Interestingly, the spectrum of *TP53* germline mutations found in LFS patients reflects those found in sporadic tumors, suggesting the importance of TP53 inactivation in tumorigenesis [17].

As one of the most well-recognized cancer predisposition syndromes, LFS has been characterized by a strikingly increased risk of early-onset breast cancer, sarcomas, brain tumors, adrenocortical carcinoma, and other neoplasms [18]. Particularly, about 50% of patients with LFS develop the first tumor by the age of 40, compared with 1% in the general population, and 90% of the carriers are diagnosed with cancer by the age of 60 [19]. In a retrospective study of 200 cancer-affected LFS individuals who survived childhood malignancies, 15% developed multiple primary cancers over their lifetimes [20].

Although the molecular basis of tumor predisposition in LFS is still a matter of debate, several potential mechanisms have been described since the identification of *TP53* mutation in 1990. In the setting of LFS, although not exclusively, the risk of tumor is specifically and significantly related to germline mutation of *TP53*, regardless of tumor type [16]. Germline *TP53* mutation–associated cancer eventually develops in 73% of men and almost 100% of women who carry such mutations, with the higher penetrance in the latter predominantly attributable to breast cancer. Analyses of genomic instability in fibroblasts established from LFS carriers have revealed that TP53 loss of function may increase spontaneous mutation activities which could lead to high rates of chromosomal instability and an allelic loss of key tumor-suppressor genes because these LFS fibroblasts spontaneously immortalize [21]. In 2006, *TP53* germline mutation carriers have been found to have a higher prevalence to carry single-nucleotide polymorphism (SNP) 309 (T > G variation) in the murine double-minute 2 (*MDM2*) gene [22]. MDM2 is a key negative regulator of TP53 that increases protein turnover through proteasomal degradation. The SNP 309T > G variation located in the first intron of *MDM2* increases Sp1 transcription factor binding and consequently the MDM2 expression levels. This augmented negative feedback loop further aggravates the haploinsufficiency of TP53, thus making the LFS patients who have SNP T309G in *MDM2* suffer an even earlier onset of tumor formation. Conversely, a higher occurrence rate in TP53-negative patients with the *MDM2* SNP 309 G allele also suggests the loss of TP53-related protection against potential genotoxic mutations in LFS patients.

In addition, *TP53* mutation in LFS has also been demonstrated to be associated with severe chromosomal aberrations and aneuploidy. TP53 is involved in the very processes known to give rise to copy number variations (CNVs), which has a 100–10,000 times higher natural occurrence rate than point mutation in the human genome [23]. Defective TP53 has been linked to an increased CNV and genomic instability in tumors. Similarly, LFS fibroblasts have a tendency of a loss of chromosomal regions containing genes involved in cell-cycle control or senescence [24]. In addition, large-scale comparative genomic hybridization studies have revealed that the CNV frequency is remarkably similar among healthy individuals but is significantly increased in LFS patients with germline *TP53* mutation [25]. LFS patients with *TP53* germline mutation present a broad spectrum of copy number alterations affecting multiple loci, including exceptionally large deletions or duplications [26]. The CNVs in p53 mutation carriers themselves frequently encompass cancer genes. In 2012, a large *BRCA1* intragenic deletion related to germline *TP53* mutation was reported in breast cancer patients previously diagnosed with LFS [27].

3.2 MYH-Associated Polyposis and Deficiency in Base Excision Repair

One of the major roles of BER in the maintenance of genome stability is to correct subtle modifications of DNA induced by reactive oxygen species (ROS)-related DNA damage which generates 8-oxoguanine products (8-oxoG). A misincorporated oxidized guanine can mismatch with adenine (Hoogsteen base pair), resulting in G:C to T:A transversion and a consequent point mutation. The codon GAA in particular is more susceptible to such mutational event which will lead to a stop codon (TAA) on condition that BER is nonfunctional. In humans, the repair of misincorporated 8-oxoG is primarily orchestrated by three proteins. The DNA glycosylase OGG1removes the 8-oxoG from 8-oxoG:C base pairs in duplex DNA; the MYH

(MUTYH) DNA glycosylase excises adenine residues mismatching unrepaired 8-oxoG replication, while MTH1 is an 8-oxo-dGTPase which hydrolyzes 8-oxo-dGTP preventing its re-incorporation into a newly synthesized DNA during the patching step of BER [4].

In 2002, biallelic mutation of the *MYH* gene (alias: *MUTYH* located on chromosome 1p32.1–p34.3) was linked to an autosomal recessive CRC predisposition syndrome associated with multiple colonic polyps [28]. More than 80 germline variants have been reported with the deleterious missense mutations Y165C and G382D account for more than 80% of mutations occurring in affected individuals with a Caucasian background. Excess risk of colon cancer occurs in biallelic *MYH* mutation carriers, of whom about 70% carry both Y165C and G382D mutations. Jenkins et al. reported a 3-fold increase in risk for colorectal cancer in monoallelic carriers and a 50-fold increase in risk in biallelic carriers (the 8% and 80% cumulative risk to age 70 years, respectively) [29]. The *APC* gene has been suggested as a major target of MYH mutation-related BER deficiency, probably due to its rich in GAA codon [28]. The rate of spontaneous G:C to T:A transversions in the *APC* gene is significantly higher in colorectal tumor cells with biallelic *MYH* mutation compared to tumor cells with intact *MYH* [30]. Concordantly, many MYH-associated polyposis patients elicit a comparable phenotype to those suffering classic or attenuated familial adenomatous polyposis (FAP) which is hallmarked by the mutated *APC* gene and hyperactivation of the β-catenin/TCF pathway [31]. In addition, G:C to T:A transversions have also been described in the proto-oncogene K-Ras, resulting in a point mutation of G12C in K-Ras. Such K-Ras mutations have been associated with a poor prognosis in colorectal cancer patients [32].

3.3 Xeroderma Pigmentosum and a Deficiency in Nucleotide Excision Repair

XP is an autosomal recessive disorder characterized by an extreme sensitivity to ultraviolet light, hyperpigmentation of the sun-exposed area, neurodegeneration, and a greatly elevated incidence of skin cancers. Compared to the general population, XP individuals have a 10,000-fold increase in the incidence of developing nonmelanoma tumors and a 2,000-fold increase in the incidence of melanoma before the age of 20 in the sun-exposed tissues such as the skin, eyes, lips, and the tip of the tongue [33]. The median age at first diagnosis of skin neoplasm for XP individuals is 8 years, nearly 50 years younger than that found in the general population. XP also manifests a 10–20-fold increase in the risk of internal neoplasms such as lung cancer [34], which may be attributed to a higher susceptibility to environmental carcinogens such as tobacco.

Although XP presents itself as heterogeneous clinical features with eight different subtypes, most of the molecular background of XP indicates defects in NER. The DNA molecule has a strong absorption of both UV-B and UV-C which have a wavelength ranging from 280 to 320 nm and 240 to 280 nm, respectively. Upon exposure to UV radiation, DNA in epidermal cells tends to form two major photoproducts: cyclobutane pyrimidine dimers (CPD) and pyrimidine (6–4) pyrimidone photoproducts (6–4 PP) that involve both T and C pyrimidines. These pyrimidine dimer-related DNA lesions require an excision of single-stranded regions of DNA by the NER system rather than BER that shows a high efficiency for small-nucleotide adducts such as methylation or incorporation of apurinic/apyrimidinic nucleotides. Large DNA adducts such as CPD and 6–4 PP, if left unrepaired, will induce DNA conformational changes and subsequently transcription and replication failure which will lead to cell senescence, apoptosis as well as mutation accumulation to promote carcinogenesis [35]. Indeed, XP presents a unique model for analyzing the effects of unrepaired DNA lesions in skin carcinogenesis. The skin cancer predisposition observed in XP patients has been attributed to eight genes, of which each point missense mutation resulted in an XP subtype. Seven of these genes, namely *XPA* (9q22.3), *XPB/ERCC3* (2q21), *XPC* (3p25), *XPD/ERCC2* (19q13.2–q13.3), *XPE/DDB2* (11p11–12), *XPF/ERCC4* (16p13), and *XPG/ERCC5* (13q33), are required to remove UV damage from the DNA. The eighth one (XPV/POLH or DNA Polη) is required to replicate the DNA containing unrepaired damage. Eukaryotic NER includes two major branches, transcription-coupled repair and global genome repair [6,7]. Transcription-coupled NER specifically induced by the damaged DNA that blocks the progression of RNA PolII and efficiently repairs DNA lesions present on the transcribed strand of actively expressed genes. Conversely, global genome repair is an RNA transcription-independent, random process that inspects the entire genome for damage and is therefore critical in protecting the nontranscribed–regulatory DNA sequences from UC-induced damages. The NER pathway eliminates DNA legions by a multi-step "cut and patch" reactions, including the recognition of helix distortions (by XPE and XPC), DNA-damage verification (by XPA), unwinding of the DNA from around the lesion (by XPB and XPD along with the TFIIH protein to prime excision of damaged DNA), DNA cut (by XPF and XPG for 5′ and 3′, respectively), and finally resynthesis for gap filling (by DNA Polδ, DNA Polκ, or DNA Polε) and DNA ligation (such as DNA ligase III).

It is clear that UV exposure is one if not the foremost risk factors for all three major subtypes of skin cancer, including a basal cell carcinoma, squamous cell carcinoma, and melanoma. The photochemistry of DNA actually leaves a characteristic fingerprint on the mutation spectrum known as UV-signature mutation. In general, dipyrimidine sites, particularly the 3′C of a TC or CC site, are most susceptible to UV-induced mutation due to the inclination of deamination in the C–C

photo-adduct leaving a C>T transition. Indeed, the analysis of type A to G XP tumors that have the defective NER capacity shows that the unrepaired DNA lesions result in higher levels of C to T and the UV signature tandem mutation CC to TT. Conversely, although the mechanism has not been fully revealed, mutation frequencies from UV damage are also increased in cells that lack POLH/XPV which encodes the class-Y polymerase capable of bypassing dipyrimidine DNA lesion to continue DNA replication. This explains the phenotype of Type-V XP which is hallmarked by defects in *POLH/XPV* gene but still can have an intact NER pathway.

UV signature mutations in several oncogenes and tumor-suppressive genes have been demonstrated to be implicated in XP-related tumor predisposition. The examination of mutations in the *TP53* gene in tumors from XP individuals reveals the C>T UV-signature mutations at a rate of more than 90% [36]. In contrast, the *TP53* mutation rate observed in sporadic skin tumors is 50%. In addition, $p16^{INK4a}$ and $p14^{ARF}$, both of which participate in the p53-related control of cell cycle, are also susceptible to UV-induced deleterious mutations in XP cells [37]. On the other hand, active mutations in all three Ras oncogenes, in particular in *N-ras*, have been observed at an approximately doubled rate in XP-related skin cancer compared to skin cancer in non-XP population (50% vs. 25%) [36]. Finally, it is important to note that the hyperactivation of the mitogenic sonic hedgehog (SHH) pathway has been associated to the initiation of skin basal cell carcinoma (BCC) in patients with XP background [38]. Germline mutations of the *PTCH* gene, one of the major components of a negative regulator of the SHH pathway and therefore a tumor-suppressor gene, have been identified to have UV-induced mutation in about 90% of XP-related BCC, which is significantly higher than the somatic mutation rate of 10–40% in non-XP BCC. In addition, significantly higher rates of UV-signature mutation in BCC from XP individuals have also been observed in two positive regulators of the SHH pathway, namely Shh (the ligand, ~20% in XP-BCC vs. <1% in sporadic BCC) and Smo (GLI1/2 transcription factor activator, ~30% in XP-BCC vs 10–15% in sporadic BCC) [36].

3.4 Hereditary Cancers Associated With Defects in DNA Mismatch Repair

Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is one of the commonest forms of inherited predisposition to colorectal cancer (CRC) accounting for 2–5% of all CRCs. CRC in individuals with Lynch syndrome differs from sporadic CRC by an earlier age of diagnosis (in the mid-40s). Individuals with Lynch syndrome have a probability of 70% to develop CRC by the age of 70 years. In contrast, the risk in the general population is around 5%. Moreover, Lynch syndrome–affected individuals are at an increased risk of a number of extra-colonic malignancies. The lifetime risk of endometrial adenocarcinoma is 30–60% (<3% in the general population) diagnosed at an average age of 40 years. Gastric, hepatobiliary tract, urinary tract, ovarian, and small bowel carcinoma have also been documented as Lynch syndrome–related malignancies with the cumulative lifetime risk at 19%, 18%, 10%, 9%, and 4%, respectively [39]. In addition, multiple sebaceous skin tumors occur in a subgroup of HNPCC, the Muir-Torre syndrome [40].

Lynch syndrome is primarily attributed to deleterious germline mutations in MMR genes, including *MLH1* at 3p21.3, *MSH2* at 2p21-22, *MSH3* at 5q11-12, *PMS1* at 2q31-33, *PMS2* at 7p22, and *MSH6* at 2p16, which lead to the loss of expression of one or more of the MMR proteins. In HNPCC, the most frequently affected genes are *MSH2* (52%), *MLH1* (22%), MSH6 (13%), and *PMS2* (9%)*, with PMS1 and MSH3 gene being* occasionally involved [41]. In another study, *MLH1* and *MSH2* account for more than 90% of the MMR mutations in Lynch syndrome families [42]. The mutational profile of MMR genes spans from point missense or nonsense mutations to large deletions and rearrangements which compromise 5–10% of *MLH1* mutations and more than 20% of *MSH2* mutations in HNPCC [43]. Several studies have revealed correlation between the MMR gene involved and the spectrum of cancer risks. Carriers of *MSH2* mutations appear to be at a higher risk of cancer than *MLH1* mutation carriers, especially for extra-colonic cancers [44]. *MSH6* germline mutation has been reported to have a particularly strong association with endometrial cancer (a lifetime risk of about 70%), yet a lower penetrance for other Lynch syndrome–related malignancies including CRC [45]. In most of cases, one mutated allele with the affected MMR gene is inherited, the loss of heterozygosity (LOH) then happens somatically to inactivate the second allele in the form of mutation, methylation, or a combination of both. It is worth to note that one mutated allele is sufficient to confer an increased risk of cancer, thus making Lynch syndrome a dominant hereditary disease. In rare cases where both inherited alleles are mutated leading to constitutional mismatch repair deficiency (CMMR-D), patients will have a phenotype resembling neurofibromatosis type 1 with an onset of a broad spectrum of malignancies during childhood, in contrast to individuals with Lynch syndrome harboring a heterozygous mutant MMR gene allele at the age of 40–50 years [46]. In 2009, another intriguing mechanism of *MSH2* inhibition has been identified through mutation of *EPCAM,* a non-MMR gene. Germline deletions of the 3′-region of *EPCAM* cause transcriptional read-through which results in silencing of *MSH2* by hypermethylation and, subsequently, the development of a MMR-deficient phenotype [47].

The strong mutator phenotype and high-frequency microsatellite instability (MSI-H) resulted from MMR deficiency has been demonstrated to be the primary source of tumor predisposition within Lynch syndrome. Microsatellites are short

tandem (1–6 base pairs) repeated DNA sequences such as $[A]_n$ or $[CA]_n$ that are present in large numbers in both noncoding and coding sequences in the eukaryotic genome. During DNA synthesis, the primer and template strands in a microsatellite (sometimes termed as "slippery DNA") can occasionally dissociate and re-anneal incorrectly [48]. This gives rise to heteroduplex DNA molecules presenting a different number of tandem-repeats in a newly synthesized strand and the template strand. These heterogeneities are known as insertion/deletion loops (IDLs) due to the aberrant conformation of unpaired nucleotides. Together with base:base mismatches arisen from sporadic escaping the proofreading function of DNA polymerase, IDLs are corrected by the MMR system which excises erroneous nucleotides of the newly synthesized strand and therefore provides the DNA polymerase with another chance to generate an accurate copy of the template sequence. In the absence of MMR, replication errors are left uncorrected and accumulated, thus leading to the creation of novel microsatellite that can be readily detected by PCR-based assays for the evidence of MSI.

Several tumor-suppressor genes contain simple repeated sequences or microsatellites in their coding sequence, including receptor kinases (eg, transforming growth factor beta receptor II/TGFBR2, activin receptor 2/ACVR2, and ephrin receptor B2/EPHB2), cell proliferation regulators (PTEN, GRB1, TCF-4, and WISP3), apoptosis inducers (eg, BAX, BCL-10, FAS, and APAF1), and DNA repair (MLH3, MSH3, MSH6, MRE11, RAD50, BLM, MBD4, and CHK1) [49,50]. Coding MSI in genes implicated in tumorigenesis causes frameshift mutations and functional inactivation of affected proteins (eg, through the generation of premature translation termination codons), thereby providing a selective growth advantage to MMR-deficient cells. Remarkably, every human MMR gene except *MLH1* includes a mononucleotide repeat. It is thus conceivable that the deficiency of MMR could be exacerbated with cumulative losses of components on the system [51]. Nevertheless, few studies have clarified which mutations of genes potentially affected by MSI-H are of a functional significance in an early tumor onset in Lynch syndrome individuals.

Several genes have been identified to be relevant for the initiation and/or progression of MSI-H-mediated tumorigenesis. The first gene in such category is *TGFBR2* in CRCs. The mutational inactivation of *TGFBR2* occurs in about 30% of colon cancers and promotes the formation of colon cancer by abrogating the antiproliferative activity of the TGF-β signaling pathway. Human colon cancer cell lines with high rates of MSI were found absent of TGFBR2 expression which is critical for TGF-β ligands to exert their antiproliferative functions [52]. The most frequent mutation is the 1-bp deletion in a tract of 10 constitutive adenines in the third exon of the gene, resulting in a truncated nonfunctional TGFBR2 protein. Clinically, *TGFBR2* mutation occurs in more than 90% of CRC cases showing MSI-H arisen from either hereditary or sporadic mutation of MMR genes. The pro-apoptotic gene *BAX* that has a long repeat of eight guanines is another gene that is commonly mutated in MSI-H CRC or endometrioid tumors [53]. Frameshift mutation of *BAX* has been detected in more than 50% of HNPCCs [54]. Activated by p53, BAX exerts its effects in the process of apoptosis to remove cells with extensive genomic legions. In HNPCC cells, the loss of function in BAX genes can result in the accelerated cancer development, even with wild-type p53 [54].

3.5 Hereditary Cancers Associated With Defects of DNA Double-Strand Break Repair

3.5.1 Ataxia–Telangiectasia (Louis–Bar Syndrome) and ATM

Ataxia-telangiectasia (A–T) is an autosomal recessive disorder that is characterized by progressive neurodegeneration, oculocutaneous blood vessels, and immunodeficiency due to a disrupted maturation of T and B cells, hypersensitivity to ionizing radiation, and a marked predisposition to malignancies. One-third of all A–T patients will develop cancer, and 15% will die of cancer. Overall, an A–T patient has a 50-fold to 150-fold excess risk to develop cancer (non-Hodgkin lymphoma or leukemia in particular) than individuals in the general population. Increased rates of breast cancer, gastric cancer, medulloblastomas, basal cell carcinomas, gliomas, ovarian cancer, and uterine cancer have been reported [55]. The A–T phenotype is caused by mutations of both alleles of the ATM gene (located in chromosome 11q22–23) that frequently result in a truncated nonfunctional gene product. Heterozygous carriers of an altered ATM allele appear to be clinically normal but are reported to be at an increased risk of developing cancer, especially in the breast [56].

A–T has been categorized as a hereditary genomic instability syndrome. This disorder involves a marked defect in sensing and responding to DNA DSBs, the most severe type of DNA damage. DNA DSBs can be generated by physiological processes such as meiotic recombination and V(D)J and class switch recombination during lymphocyte maturation, ionizing radiation, free radicals as well as genotoxic reagents that generate nicks, adducts, or intercalation leading to a collapse of stalled replication forks. Such genotoxic reagents include DNA topoisomerase inhibitors (eg, camptothecin and doxorubicin), DNA intrastrand and interstrand cross-linking reagents (eg, hydroxyurea, mitomycin, cisplatin, and nitrogen mustards), and PARP inhibitors (through the accumulation of SSBs). DNA DSBs represent a major disruption in

the integrity of the genome. If not repaired correctly, DSBs can cause deletions, translocations, and fusions in the DNA. It is therefore conceivable that the ATM-deficient A–T immature lymphocytes are incapable to repair DNA DSBs that are generated during V(D)J recombination, resulting in unaccomplished T-cell and B-cell ontogeny and a consequent immunodeficiency [57].

The major known role of ATM is to participate in the responses to DNA DSBs for DNA repair and cell-cycle checkpoint activation. Upon DSB, ATM is rapidly recruited at the site of break through interacting with the MRN (MRE11-RAD50-NBS1) complex as well as the regions that flank the break. In the flanking regions, the activated ATM phosphorylates p53 and CHK2 so that G1/S checkpoint or S-phase checkpoint can be initiated to facilitate DNA repair. Notably, the activation of p53 is defective in A–T cells, resulting in failure to activate the G1/S checkpoint upon irradiation-induced DSB [58]. In addition, ATM also signals to the DNA-repair machinery to assist in the repair of DNA DSBs.

3.5.2 Hereditary Cancers and the FA/BRCA Pathway

Hereditary breast and ovarian cancer (HBOC) and FA are two inherited syndromes arising primarily from defects in DNA repair. Proteins encoded by the BRCA and FA genes form a conserved DNA-repair pathway known as the FA/BRCA pathway which removes interstrand cross-links and DSBs by HDR [59,60]. So far, 15 genes have been found being mutated in FA patients, including *FANCA*, *B*, *C*, *D1* (*BRCA2*), *D2*, *E*, *F*, *G*, *I*, *J* (*BRIP1*), *L*, *M*, *N* (*PALB2*), *O* (*RAD51C*), and *P* (*SLX4*). Upon replicative stresses, seven of the 15-gene-encoded FA proteins, including FANCA, B, C, E, F, G, L, and the FA-associated protein (FAAP100) assemble the FA core complex [61]. Upon stalled DNA replication, the interstrand cross-link (ICL) is recognized by FANCM and the associated proteins, then the latter will recruit the FA core complex that monoubiquitinates other two FA proteins, FANCD2 and FANCI. These ubiquitinated FANCD2 and FANCI proteins in chromatin recruit endonucleases (eg, Fanconi-associated nuclease 1, FAN1) and DNA polymerases for translesion DNA synthesis (Polε, Polκ, Polι, and Polν) that are required for the repair process. In coupled with translesion DNA synthesis, the interstrand adduct was removed sequentially from the antisense and sense strand by nucleases involved in NER, leaving a temporary DNA DSB. Next, the ubiquitinated FANCD2-FANCI recruits three downstream FA proteins (FANCD1/BRCA2, FANCN/PALB2, FANCJ/BRIP1, and BRCA1) to initiate homology-directed DNA repair (HDR) to remove the DSB. Finally, FANCM recruits the Blm helicase, and together they resolve the intermediate structure and reinstate DNA replication [61]. It is worth to note that, in addition to participating in resolving the intermediate DSB in DNA interstrand cross-linking repair as a positive regulator of DNA homologous recombination, FANCD1/BRCA2, FANCN/PALB2, FANCJ/BRIP1, and BRCA1 are also crucial in repairing DNA replication-independent DSBs, including ionizing radiation–induced DNA lesions. Deficiencies of these genes have been associated with an increased susceptibility of neoplastic transformation such as in hereditary breast and ovarian cancer.

Germline mutations in *BRCA1* and *BRCA2* genes are responsible for only 2–5% (up to 10%) of all breast and ovarian cancers [62]. However, these mutations account for about 50% and 45% of all hereditary breast and ovarian cancers, respectively [59]. A 2003 meta-analysis using pooled pedigree data from 22 studies involving 8139 index cases indicated that the average cumulative risk for *BRCA1*-mutation carriers to develop breast or ovarian cancer by the age 70 was 65% (44–78%) and 39% (18–54%), respectively [63]. The corresponding analysis for *BRCA2*-mutation carriers showed a 45% (31–56%) lifetime risk of developing breast cancer and a11% (2.4–19%) lifetime risk of developing ovarian cancer. In 2008, an analysis using data from 155 *BRCA1* and 164 *BRCA2* mutation carrier families in Spain showed the similar average cumulative risks of breast and ovarian cancers [64]. Furthermore, a significantly increased risk of other cancers has also been noted in *BRCA*-mutation carriers, such as stomach, pancreas, prostate, colon, and hematologic cancers [62,65]. For example, loss-of-function mutations of *BRCA* genes have also been associated with an increased risk of developing leukemia and lymphoma (up to 2000-fold) [65]. Interestingly, *BRCA1* and *BRCA2* mutation carriers are eventually characterized by tumor phenotypes. The majority of breast cancers that arise in *BRCA1* mutation carriers are triple-negative loss of function in estrogen receptor (ER), progesterone receptor (PR), and tyrosine kinase-type cell surface receptor HER2 (HER2/ERBB2) [66]. However, tumors arising in *BRCA2* mutation carriers are most frequently ER- and PR-positive. Although a number of studies showed a better prognosis and a 5-year survival in patients with breast or ovarian cancer arising in *BRCA* mutation carriers compared to sporadic cancers, growing evidence also indicated no difference in survival rate between *BRCA* mutation carriers and noncarriers [67], suggesting that further studies are essential to evaluate whether *BRCA* mutation could act as an independent favorable prognostic factor for breast cancer clinical outcome. It is believed that the functional status of DNA-repair pathways may impact the cancer cell response to anticancer chemotherapy. As demonstrated by several lines of evidence from both clinical and laboratory-based studies, a hereditary or sporadic loss of function in BRCA1, BRCA2, PALB2, and BRIP proteins (termed as BRCAness) implicates a susceptibility to platinum and other genotoxic agents in breast and ovarian cancers due to an inadequate homology-directed DNA repair [68,69]. Moreover, the additional inhibition

of other DNA-repair pathways may potentiate the extent of DSB and consequently lead to synthetic lethality in HDR-deficient cells. This has been employed in the treatment of "BRCAness" breast and ovarian cancers with PARP inhibitors and revealed promising results.

FA is one of the rare hereditary bone marrow failure syndromes with an increased susceptibility to cancer, including leukemia [70], due to the biallelic mutation in FA genes [60]. The incidence rate of FA is about 1 in 100,000 births [71]. Generally, the majority of FA patients are identified as young children due to the presence of physical anomalies, such as short stature, café au lait spots and hyper/hypopigmentation, cytopenias, abnormal thumbs, microcephaly, micro-ophthalmia, and so on. However, up to a quarter of patients with the FA gene mutations display a normal phenotype [72]. Yet the mechanisms involved in FA have not been completely understood. Biallelic germline loss-of-function mutations of genes in the FA/BRCA pathway may contribute predominantly to the initiation and progress of FA. The knockdown of FANCA and FANCD2 in human embryonic stem cells using RNAi results in defects in the early development of hematopoietic lineage [73]. FA has been linked to cancer which is one of the most frequent causes of FA-related death. The most common malignancies arising in FA patients are acute myeloid leukemia (AML), head and neck squamous cell carcinoma (HNSCC), vaginal squamous cell carcinoma, liver and brain tumors [72], representing a 600-fold increase in risk of AML, a 500-fold increase in risk of HNSCC, and a 3000-fold increase in risk of vaginal squamous cell carcinoma, compared to the general population. Although the FA pathway has been demonstrated to be functionally linked to DNA-repair pathways, yet many details remain poorly understood. A better understanding of this pathway and more detailed information on its connection to DNA-repair pathways may offer opportunities to identify diagnostic biomarkers, prognostic indicators, and therapeutic targets for the HBOC and FA syndromes.

4. GENOMIC INSTABILITY IN SPORADIC CANCERS

The vast majority of cancers are nonhereditary "sporadic cancers." Almost all of the human sporadic cancers are characterized by genomic instability, especially chromosomal instability (CIN). The heterogeneity in the extent and type of genomic instability, including nucleotide, microsatellite, or chromosomal instabilities, has been shown both within the same neoplastic tissue and between cancer types [74]. Genomic instability refers to a transient or persistent state with an increased frequency of mutations within the cancer genome or a cellular lineage. These mutations include nonsynonymous alterations in nucleic acid sequences, chromosomal rearrangements, or changes in chromosome numbers, resulting in the continuous modification of tumor cell genomes, the subsequent acquisition of additional DNA alterations, clonal evolution, and tumor heterogeneity. Therefore, genomic instability which has been observed in a range of malignant stages [75,76] has been considered as a driving force of tumorigenesis [77]—from pre-neoplastic lesions to advanced tumors.

4.1 CIN in Sporadic Cancers

Chromosomal instability is the predominant form of genomic instability that leads to changes in both chromosome numbers and structure [75]. Numerical CIN is a high rate of either gain or loss of whole chromosomes, also called aneuploidy. Normal cells make errors in chromosome segregation in about 1% of cell divisions, whereas cells with CIN increase the error rate to 20% of cell divisions [78]. By contrast, structural CIN is the rearrangement of parts of chromosomes and amplifications or deletions within a chromosome. Almost all solid tumors show CIN, and about 90% of human cancers exhibit chromosomal abnormalities and aneuploidy [79]. The features of CIN tumor include global aneuploidy, loss of heterozygosity, homozygous deletions, translocation, and chromosomal changes such as deletions, insertions, inversions, and amplifications.

CIN leads to karyotypic instability and the simultaneous growth of multiple tumor subsets, resulting in inter- or intro-tumor heterogeneity [80]. Epithelial tumors generally exhibit a greater degree of genomic instability than hematologic and mesenchymal malignancies [74]. This is supported by a finding that epithelial-derived cancers such as breast, melanoma, lung, and prostate cancers have more somatic mutations than blood cancers [81]. Notably, distinct instability phenotypes could be displayed in the same cancer type. For example, lung cancer in smokers and nonsmokers shows a different extent of segmental alterations and genome instability [82]. Moreover, lung adenocarcinoma and squamous cell carcinoma exhibit a distinct type of genomic changes. Even within lung adenocarcinomas, a greater genomic instability has been found in the magnoid subtype compared to other subtypes of adenocarcinoma [83].

Studies in 2008 suggested that CIN is associated with a poor clinical outcome in solid tumors [84]. By developing a computational model, Carter et al. have identified a chromosomal instability signature that predicts a poor survival in 12 data-sets representing six cancer types, including breast, lung, and brain tumors as well as mesothelioma, glioma, and lymphoma [85]. One explanation of the clinical relevance of CIN is that CIN may be related to an increased tumor cell

heterogeneity, thereby enhancing the ability of tumors to adapt to environmental stresses [86]. Moreover, preclinical studies have shown that CIN is associated with the intrinsic multidrug resistance both *in vitro* and *in vivo* [87].

4.2 Hypothesis of the Mechanisms of CIN

Although the fundamental importance of CIN in cancer biology has been recognized for decades, the molecular basis of CIN in sporadic cancers remains unclear. This is primarily due to the heterogeneous nature of CIN in sporadic cancers; numerous genes have been uncovered to contribute to CIN, including, but not limited to, those involved in chromosome condensation and segregation (*STAG2*) [88], sister chromatid cohesion (hSecutin) [89], cytokinesis (*MOS*, *RAS*, *RAF*) [90], telomere function (*TRF1* and tankyrase) [91], DNA damage (*TP53* and *ATM*) [92], and mitotic checkpoint (*SAC*, *BUB1*, *MAD2*) [93–95]. It is challenging to unify these often conflicting mechanisms into one general mechanism to explain CIN in human sporadic cancers.

Studies to explore the presence of genomic instability in sporadic cancers have led to three prevailing hypotheses. The first is the mutator hypothesis which states that mutations in caretaker genes (refer to the genes that primarily function to maintain genomic stability) [96] cause genomic instability in precancerous lesions and drive tumor development by increasing the spontaneous mutation rate. The second hypothesis is the oncogene-induced DNA replication stress model which demonstrates that CIN in sporadic cancers is the consequence of the oncogene-induced collapse of DNA replication forks, which in turn leads to DNA DSBs and genomic instability. The third theory states that telomere erosion and dysfunction give rise to CIN [97].

Caretaker genes encode proteins that stabilize the genome, thus mutations in caretaker genes lead to genomic instability. The classical caretaker genes are majorly of two types: DNA-repair genes and mitotic checkpoint genes. It is important to note that although the TP53 gene can be considered as a caretaker gene, TP53 is subject to selective pressure for the inactivation in cancer, whereas other classical caretaker genes are not. Therefore, when we refer to caretaker genes, TP53 is not included.

The mutator model is generally considered as the major mechanism responsible for the presence of genomic instability in hereditary cancers. Attempts to identify mutations in caretaker genes in sporadic cancers were unsuccessful in the past few years [98]. For example, in 2004, Wang et al. analyzed the sequences of 100 cell-cycle checkpoint and DNA-repair genes in early passage human colon cancer cell lines, yet they identified very few mutations [99]. Furthermore, Cahill and his colleagues generated chromosome instability in the experimental model by mutating the mitotic checkpoint gene budding uninhibited by benzimidazoles 1 (*BUB1*). However, sequencing studies showed that *BUB1* mutations were rare in human cancers [93]. To date, whole cancer genome sequencing has failed to identify putative caretaker genes that are frequently mutated in human cancer, and only 3–31% of sporadic cancers harbor at least one mutation of a caretaker gene [100]. These studies suggest that mutations in caretaker genes are not the cause, or at least a major cause, of genomic instability in sporadic cancers. Moreover, few studies convincingly support telomere erosion hypothesis. Therefore, an oncogene-induced DNA stress model is currently a generally accepted hypothesis to explain CIN in sporadic cancers, which we discuss further.

4.3 High-Throughput Sequencing Studies on CIN in Various Cancers

The development of high-throughput sequencing technologies enables researchers to investigate the genetic profiles of human cancers in a much more efficient manner. Here, we highlighted several important high-throughput sequencing studies that help us understand the molecular mechanism of CIN in several common types of human cancer such as breast, colorectal, lung cancers, and glioblastoma.

To determine the spectrum and extent of somatic mutations in human cancers, Kinzler and his colleagues sequenced 18,191 genes in genomic DNA isolated from 11 breast and 11 colorectal tumors [101]. Mutations were found in 1137 genes from breast cancers, and 848 genes from colorectal cancers. But in the additional validation screening of 24 breast and 24 colon cancers, only 167 of 1137 (14.69%) gene mutations and 183 of 848 (21.58%) gene mutations were detected. Then the same group of researchers analyzed sequences of 23,219 transcripts, representing 20,661 protein-coding genes in 24 pancreatic cancers [102]. Of 20,661 genes analyzed by sequencing, 1327 were mutated in at least one sample, and 148 were mutated more than twice among 24 cancers examined. In the subsequent validation screening, 39 genes that were mutated in more than one of the 24 cancers in the discovery set were sequenced in the additional 90 pancreatic cancers. The results of the analysis showed that 255 nonsilent somatic mutations occurred in 23 genes. Deletions and amplifications of these cancer genomes were also examined using SNP. The classical tumor-suppressor genes *CDKN2A* (encodes p16INK4A and p14ARF), *SMAD4* and *TP53,* were found mutated, whereas the small GTPase *KRAS* was found to be one of the most frequently mutated oncogenes in pancreatic cancer.

The same 20,661 protein-coding genes were also sequenced in 22 human glioblastomas [103]. The analysis results showed that 3.4% of the 20,661 genes (698 genes) were mutated at least once. Most of the mutations were single-base substitutions (94%), whereas the others were small insertions, deletions, or duplications. A set of 21 mutated genes were selected and evaluated in a second screen comprising an additional 83 glioblastomas. Nonsilent somatic mutations were identified in 16 of 21 genes in the additional tumor samples, and the mutation rates were significantly increased from 1.5 mutations per Mb in the discovery screen to 23 mutations per Mb in the consequent validation screen. The most frequently changed genes were *CDKN2A* (altered in 50% of samples); *TP53*, *EGFR*, and *PTEN* (altered in 30–40% of samples); NF1, *CDK4*, and *RB1* (altered in 12–15% of samples); and *PIK3CA* and *PIK3R1* (altered in 8–10% of samples).

Another unbiased genomic study on glioblastomas was conducted by The Cancer Genome Atlas Research Network [104]. A total of 91 matched tumor–normal pairs including 72 untreated and 19 treated cases were examined for mutations in 601 cancer-relevant genes. The results uncovered 453 validated nonsilent somatic mutations in 223 genes, and 79 of these genes were mutated twice or more. Interestingly, the frequency of mutations was remarkably different between untreated and treated tumors (98 events among 72 untreated cases versus 111 among 19 treated cases, $P < 10^{-21}$). This difference was primarily driven by seven hypermutated samples, six of which harbored mutations in at least one of the MMR genes *MLH1*, *MSH2*, *MSH6,* or *PMS2*, suggesting that mutations in caretaker genes and a decreased DNA-repair activity may subsequently occur spontaneously during tumor progression or due to genotoxic therapeutic reagents, rather than primarily contribute to the initiation of the tumor.

Lung cancer was also studied by the Cancer Genome Atlas Research Network. DNA sequencing of 623 cancer-related genes in 188 human lung adenocarcinomas discovered more than 1000 somatic mutations across samples [105]. This study identified 26 frequently mutated genes that include tumor-suppressor genes *NF1*, *APC*, *RB1,* and *ATM*. Also, the NHEJ DNA-repair gene *PRKDC* and the MMR gene *MSH6* were mutated in six and four cases, respectively. Mutations in homologous recombination-repair genes *BRCA1*, *BRCA2*, the BRCA1-associated RING domain 1 (*BARD1*), *BAP1*, the BER gene *XRCC1*, the NER gene *XPD,* and the mitotic checkpoint genes *BUB1* and *STK12* were also detected in lung adenocarcinomas.

A similar genome-wide study of the molecular basis of CIN was conducted in hematologic cancer. Whole-genomic sequencing of four representative chronic lymphocytic leukemia (CLL) cases identified 46 somatic mutations, and the further screening of 363 CLL patients found four recurrent mutations of notch1 (*NOTCH1*), exportin 1 (*XPO1*), myeloid differentiation primary response gene 88 (*MYD88*) and kelch-like 6 (*KLHL6*) [106]. The subsequent functional and clinical analyses indicated that recurrent mutations are oncogenic and associated with a poor clinical outcome.

In 2013, the mutation spectra of esophageal adenocarcinoma (EAC) have been investigated by both whole-exome (149 EAC tumor–normal pairs) and whole-genome sequencing (15 of 149 pairs) [107]. Chromatin-modifying factors and candidate contributors were found significantly mutated in EAC, including *SPG20*, *TLR4*, *ELMO1,* and *DOCK2*. A more comprehensive study on the genomic instability patterns in esophagus, stomach, and colon adenocarcinomas showed that a significant recurrent amplification and deletion of genes were distinct to various gut-derived adenocarcinomas [108].

High-throughput sequencing studies provided deeper insights on the molecular basis of CIN in human cancers. These unbiased genome-wide studies indicated that mutations in the caretaker genes were infrequent. The frequency of caretaker gene mutations ranged from 14 to 31%, depending on the tumor type [100]. Collectively, 69–97% of cancers did not have mutations in caretaker genes, suggesting that the inactivation of caretaker genes is not the major cause of genomic instability in many sporadic cancers.

4.4 Oncogenes Induce CIN

The hypothesis that the most frequently mutated or deregulated oncogenes in response to DNA damage in sporadic cancers are responsible for CIN seems to be a favorable mechanism based on the high-throughput studies mentioned earlier. The frontier studies have provided evidence for this hypothesis. In 1996, Mai et al. increased the level of c-Myc protein in Rat1A–MycER cells and investigated chromosomal aberrations [109]. This early study indicated that the upregulation of the c-Myc protein which is an important cell-cycle regulator would lead to chromosome numerical changes, chromosome breakage, chromosome fusions, and other chromosomal abnormalities. In 1999, Charles et al. showed that the overexpression of cyclin E, another important positive cell-cycle regulator and oncogene, led to CIN in both rat embryo fibroblasts and human breast epithelial cells [110]. Later studies in 2000 have suggested that the disrupted expression of cyclin E in karyotypically stable colorectal cancer cells may lead to increased CIN and consequently a more malignant phenotype [111]. This phenotype attributed to a defect in the execution of metaphase and subsequent transmission of chromosomes caused by aberrant accumulation of cyclin E. In 2006, Di Micco et al. showed that the activation of oncogene H-RasV12 in

normal cells was able to trigger cell proliferation, DNA-damage response, and cancerous transformation, both *in vitro* and *in vivo* [112]. Mounting evidences are supportive to the hypothesis that oncogenes trigger CIN.

It is important to note that CIN and neoplastic formation induced by oncogenes requires inactivation of the p53 pathway. Richard and Randy showed that oncogenic H-RasV12 was unable to induce CIN in the mouse embryonic fibroblasts (MEFs) with wild-type p53 ($p53^{+/+}$), but was capable of inducing CIN in the $p53^{-/-}$ MEFs cultured in the same conditions [113]. Furthermore, using *in vivo* mouse models, this group of investigators also found that the loss of p53 function was critical for cells to create a permissive environment allowing cancerous transformation.

Oncogene-induced CIN hypothesis highlighted the importance of the p53 protein and distinguished this molecule from other tumor suppressors. As the product of TP53, p53 has been dubbed "the guardian of the genome," and it controls cell fate after DNA damage such as DNA repair and survival or programmed death. Not surprisingly, TP53 is one of the most frequently mutated genes (>50%) in human cancer [114]. As TP53 is a DNA damage–checkpoint protein, its inactivation was expected to induce genomic instability. However, numerous studies have proved that the deletion of the TP53 gene in mouse model and human cell lines does not induce aneuploidy [115].

According to the oncogene-induced DNA replication stress model, CIN is mainly caused by DNA damage or other forms of DNA replication stress. Specific genomic loci called common fragile sites that preferentially exhibit gaps and breaks on metaphase chromosomes have been demonstrated to be more sensitive to the inhibition of DNA synthesis [116]. Previous CIN studies on human precancerous lesions and different experimental systems showed that these common fragile sites were prone to genomic instability induced by oncogenes [117].

4.5 Chromothripsis

Sporadic cancer is driven by gradually accumulated genomic alterations, such as somatic point mutations, chromosome rearrangements, and numerical and structural changes in chromosomes. Recent studies using next-generation DNA sequencing and SNP array analyses and bioinformatics methods have uncovered a new form of genomic chaos called chromothripsis (from Greek for "chromosome" (chromo) and "shattering into pieces" (thripsis)) [118]. Chromothripsis can be defined by three major features: remarkable chromosomal rearrangements in localized regions; a low degree of chromosomal gain or loss showing haploid (heterozygous deletion) or diploid across the rearranged region; and the preservation of heterozygosity.

Chromothripsis was first described by Stephens and his colleagues [119]. Using paired-end sequencing of the genome of a chronic lymphocytic leukemia (CLL) sample, they identified one patient who had 42 somatically acquired genomic rearrangements involving the long arm of chromosome 4. Although most of the rearrangements occurred in the region of chromosome 4, some of them also included segments from the regions of chromosome 1, 12, and 15. Further studies indicated that the stamp of chromothripsis can be seen in at least 2–3% of diverse cancer cell types. Moreover, chromothripsis is more prevalent in bone cancers; about 25% of osteosarcoma and chordoma exhibit features of this phenomenon.

Rearrangements generated in a single genomic crisis have shown their effects on multiple cancer-related genes. Chromothripsis in a chordoma patient showed the loss of tumor-suppressor genes *CDKN2A* (cyclin-dependent kinase inhibitor 2A), *WRN* (Werner syndrome ATP-dependent helicase), and *FBXW7* (F-box and WD-40 domain containing 7), indicating that several tumor-promoting events might occur concurrently.

Although further work is needed to fully understand these mechanisms and the prevalence of chromothripsis, some current studies have already shown the promise of its clinical implications. Studies on multiple myeloma and neuroblastoma patients have revealed the correlations of chromothripsis and a poor patient survival, suggesting that the examination of hallmarks of chromothripsis might be a novel way to identify high-risk cancer patients [120].

4.6 Microsatellite Instability in Sporadic Cancer

MSI is another form of genomic instability in sporadic cancer which is generally caused by deletions or random insertions of microsatellites [121]. Microsatellites are repetitive DNA sequences ranging from 2 to 5 base pairs that occur at thousands of locations in the human genome [121]. Microsatellites are characterized by high mutation rates and diversity in the population. MSI results from impaired MMR system, especially alterations of the *MLH1*, *MSH2*, *MSH6,* and *PMS2* genes.

MSI has been reported in numerous types of cancers, including gastric, endometrial, ovarian, lung, and colorectal cancers (CRC) [122–125]. Colorectal cancer is the first cancer type where MSI has been described and extensively studied. MSI occurs in about 15% of CRC cases that show a poorer clinical outcome compared to MSI-negative CRCs [126]. MSI is present in both hereditary and sporadic CRCs through different mechanisms. Hereditary nonpolyposis colon cancer (HNPCC, also

known as Lynch syndrome) is characterized by inactivating germline mutations of *MSH2*, *MSH6*, *PMS2,* or *MLH1,* whereas sporadic CRCs with MSI are associated with hypermethylation (CpG island methylator phenotype referred to CIMP) and the loss of MLH1 expression [127]. CIMP is characterized by simultaneous methylation of multiple CpG islands of tumor-suppressor genes, such as *MLH1*, *CDKN2A,* and *THBS1* [127,128].

Genomic instability has been accepted as the major cause that plays a central role in sporadic cancer development, although our understanding of the molecular basis of genomic instability is very limited. It is contradictory about the process, timing, and extent of genetic alterations that occur in cancer: tumorigenesis could be the result of the accumulation of several genetic errors; or it could be due to multiple genetic alterations in a single catastrophic event, chromothripsis. Compared to other forms of genetic alterations, CIN is the dominant phenotype that may result from the gain-of-function alteration, rather than the inactivation of caretaker genes. The importance of CIN in sporadic cancer should make it a top priority in cancer biology research that provides promise for the improved therapeutic strategies.

5. TRIGGERING EXCESSIVE GENOMIC INSTABILITY BY TARGETING DNA-REPAIR PATHWAYS AS A STRATEGY FOR CANCER THERAPY

In the last three decades, one of the significant advances in our understanding of the mechanisms involved in the maintenance of genome integrity is the discovery of members of the poly(ADP-ribose) polymerase (PARP) gene family, such as *PARP1*. Proteins encoded by *PARP* genes have been demonstrated to be crucial in the repair of DNA SSBs resulted from direct DNA oxidization, BER, or erroneous topoisomerase activity at a rate of three orders of magnitude more frequently than DSBs. PARP proteins exert their function by directly binding to SSBs and promoting a rapid access by, and the accumulation of, downstream repair factors such as XRCC1 [129]. To date, as many as 17 mammalian PARP family members have been identified [130], while only a few, such as PARP1-4, TNKS (TRF1-interacting, ankyrin-related ADP-ribose polymerase), and TNKS2, display an enzymatic activity that catalyzes the poly(ADP-ribosyl)ation of nuclear proteins. The well-defined structure of PARP1 is primarily composed of three functional domains, including a DNA-binding domain (DBD), an automodification domain (AD), and a catalytic domain (CD) (Fig. 27.4A) [131].

Once activated by DNA damage, PARP1 forms a homodimer that can recognize a DNA lesion via its DBD domain (Fig. 27.4B). Using NAD^+ as a substrate, PARP1 catalyzes the poly(ADP-ribosyl)ation on acceptor proteins, such as histones and PARP1 itself. PARP1 loses its DNA-binding affinity due to the net negative charge of poly(ADP) ribose (pADPr, yellow beads); as a result, pADPr recruits other repair proteins to the site of the damaged DNA (blue and purple circles, Fig. 27.4B) [131], for instance, XRCC1, histone H1, Ku70, and Ku80, thus allowing them to repair the damaged DNA. The pADPr chain is then hydrolyzed into ADP-ribose units by poly(ADP-ribose) glycohydrolase (PARG) and/or ADP-ribose hydrolase 3 (ARH3). The ADP-ribose is further converted into AMP by pyrophosphohydrolase NUDIX, increasing AMP:ATP ratios and consequently leading to the activation of AMP-activated protein kinase (AMPK) for further adaptive stress responses such as metabolic control and pro-survival autophagy [131].

In contrast to other components of the DNA-repair machinery, such as BRCA1/2 mediating the homology-directed DNA DSB repair, that are frequently inactivated during the initiation and progression of hereditary and sporadic cancers, PARP1, the key player in the BER pathway for repairing DNA SSBs has been demonstrated to be upregulated in various human malignancies, such as breast cancer [132]. PARP1 overexpression has been associated with a higher tumor grade, estrogen independence, and a worse metastasis-free survival, implicating an oncogenic role of PARP1 in breast cancer. The oncogenic characteristics of PARP1 may contribute primarily to cancer cell survival via DNA repair to maintain the cellular homeostasis by removing DNA lesions resulted from intrinsic replication errors, metabolic damage, and, more importantly, extrinsic stresses through genotoxic therapeutic reagents because excessive genomic instability is detrimental and can usually lead to cell death [133].

The development of therapeutic reagents that specifically target malignant cells has been proved difficult. However, the concept of synthetic lethality has begun to shed some light on targeting certain malignancies with defined genetic defects [134]. Synthetic lethality is known as a phenomenon upon which cell death can be induced by combined genomic abnormalities (either a gain of function or a loss of function) of two distinct pathways, whereas a dysfunction in either pathway alone has no significant effect on viability. One of the most studied models for synthetic lethality is the particular susceptibility to PARP inhibitors in cells lacking HDR-mediated DNA double-strand repair. Several independent studies have demonstrated that the deficiency of key HDR genes, such as BRCA1 and BRCA2, profoundly sensitizes tumor cells to PARP inhibitors [135], resulting in chromosomal instability, cell-cycle arrest, and apoptosis. The potential mechanism of the hypersensitivity to PARP inhibitors in HDR-deficient cells may be attributed to the persistence and accumulation of DNA DSBs derived from unrepaired SSBs during DNA replication (Fig. 27.5). Conversely, cells with functional HDR elicit a final safeguard to efficiently prevent the cytotoxic DSB accumulation when treated with PARP inhibitors, allowing damaged DNA to be replicated and repaired by error-prone DNA polymerases. Considering the prevalence of germline and

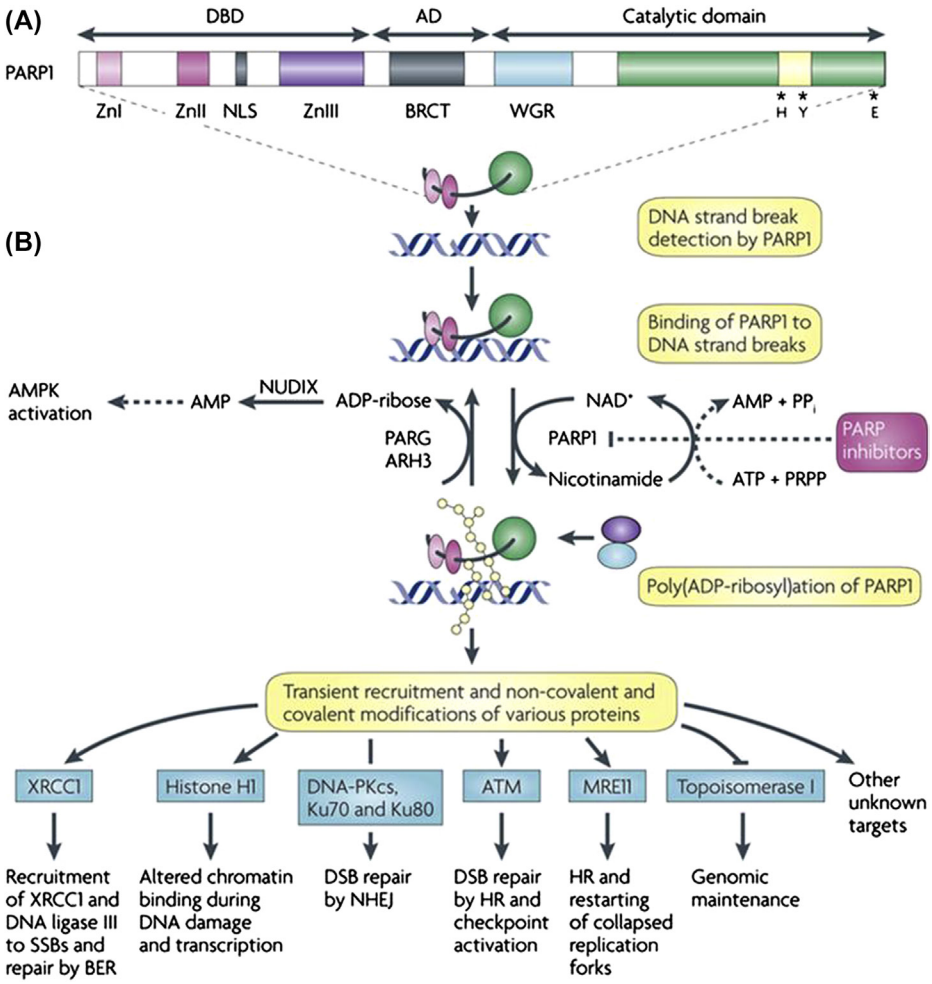

FIGURE 27.4 **Structural and functional features of poly(ADP-ribose) polymerase 1 (PARP1).** (A) PARP1 structure. (B) Biological functions of PARP1. The asterisk indicates essential residuals for NAD^+ binding (H, histone; Y, tyrosine) and polymerase activity (E, glutamic acid). *Adapted from Rouleau M, et al. PARP inhibition: PARP1 and beyond. Nat Rev Cancer 2010;10(4):293–301. We thank Nature Publishing Group's for permission, http://www.nature.com/nrc/journal/v10/n4/full/nrc2812.html.*

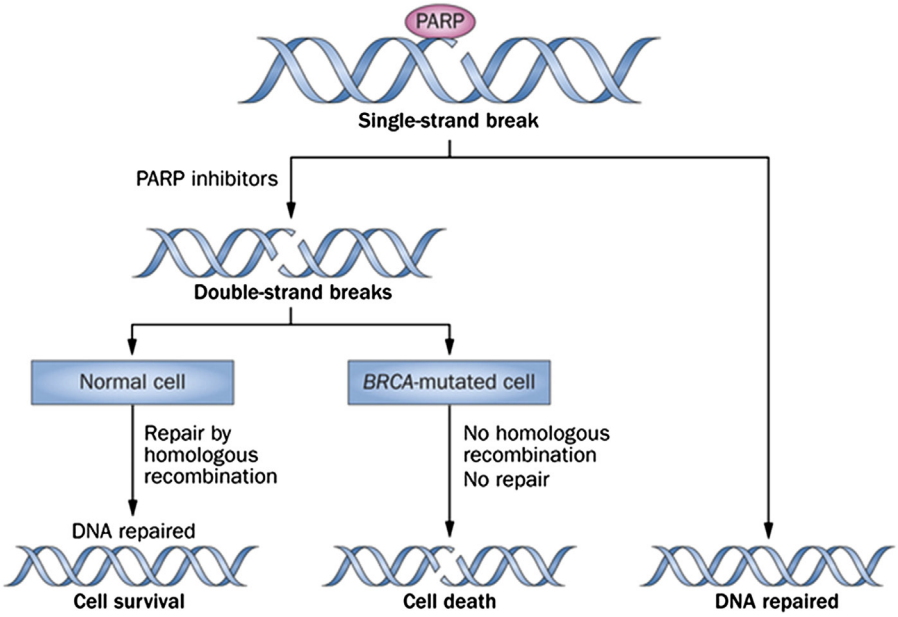

FIGURE 27.5 **Synthetic lethality induced by PARP inhibitor.** *Adapted from Sonnenblick, A, et al. An update on PARP inhibitors—moving to the adjuvant setting. Nat Rev Clin Oncol 2015;12(1):27–41. We thank Nature Publishing Group's for permission, http://www.nature.com/nrclinonc/journal/v12/n1/full/nrclinonc.2014.163.html.*

sporadic mutations of HDR-related genes such as *BRCA1* and FA pathway–related genes in various types of malignancies, the synthetic lethality may therefore represent a new direction in anticancer drug development [136].

Owing to the unique antitumor features, the development of selective and effective PARP inhibitors has become an active area in drug discovery. To date, more than 30 clinical trials have been reported to evaluate PARP inhibitors in different phases in treatment of a variety of carcinomas [137,138]. PARP inhibitors have been used as either monotherapeutic agents to induce synthetic lethality in HDR-deficient cancers such as breast, ovarian, and prostate cancers, or they can be combined with other DSB-inducing chemo- and/or radio-therapies to potentiate the therapeutic efficacy in glioblastoma, melanoma, head and neck cancers [138].

However, it should be noted that in the majority of *BRCA1*-mutant cancers (>80%), *p53* was also mutated [139]. The mutated p53 may nullify the apoptotic pathway mediated by p53 that could account for synthetic lethality of most BRCA1-deficient carcinomas, unless the PARP inhibitors induce a p53-independent apoptosis. In addition, although PARP1 and PARP2 are primarily involved in SSB repair, diverse functions of the PARP family members have been demonstrated in a wide range of biological processes [137]. Further investigations are required for better understanding of the molecular mechanisms underlying PARP inhibition.

6. CONCLUSION

Genomic instability has been accepted as the major cause that plays a central role in cancer progression, although our understanding of the molecular basis of genomic instability is very limited. DNA-repair pathways are pivotal processes in the maintenance of genomic stability. Thus, it comes as no surprise that any events leading to a deficiency in these pathways will increase susceptibility to cancer. Although the molecular basis of genomic instability is well defined in inherited cancers owing to the established relationship between mutations in DNA-repair genes and tumorigenesis, it is poorly understood in sporadic cancers. However, the importance of CIN in sporadic cancer should make it a top priority in cancer biology research and provide promise for the improved therapeutic strategies. The direct evidence showing that the genomic instability is the driving force for cancer development is scanty, which is partially due to the lethal effect of germline mutations, especially tumor suppressors, on the development of model animals before tumor formation. However, the recently developed conditional knockout technology may effectively overcome these challenges. Although targeting DNA-repair pathways has been shown as a novel and promising strategy for cancer therapy, further studies in different types of human cancer are required to better understand the underlying mechanisms of drug resistance and refractoriness, so that the therapeutic efficacy can be further potentiated.

GLOSSARY

BRCAness refers to germline or sporadic mutation of BRCA1, BRCA2, or other Fanconi anemia genes which results in deficiency in homology-directed DNA repair and cancer susceptibility. Tumor cells with BRCAness are particularly sensitive to genotoxic anticancer reagent such as platinum and PARP inhibitors.

Haploinsufficiency refers to a situation in diploid organisms that a single copy of wild-type gene is by itself incapable to maintain normal function due to the reduced expression of corresponding transcripts. Haploinsufficiency is one of the major causes of certain dominant inherited diseases, as a heterozygosity or hemizygosity elicits significant phenotypic impacts.

Slippery DNA refers to certain DNA sequences rich in single-nucleotide repeats or tandem repeats (microsatellites) at which the replicating DNA polymerase is error prone to potentiate microsatellites instability if replicative errors are left unfixed by the DNA mismatch repair.

LIST OF ABBREVIATIONS

ACVR2 Activin Areceptor type 2A
AD Automodification domain
AML Acute myeloid leukemia
AMPK AMP-activated protein kinase
AP Apurinic/apyrimidinic
APAF1 Apoptotic protease activating factor 1
APC APC gene
APE1 AP endonuclease 1
APTX Aprataxin
ARH3 ADP-ribosyl hydrolase 3
ATM Ataxia-telangiectasia-mutated gene

BAP1 BRCA1-associated protein 1
BARD1 BRCA1-associated ring domain 1
BAX BCL2-associated X protein
BCC Basal cell carcinoma
BCL10 B-cell CLL/lymphoma 10
BER Base excision repair
BLM BLM gene
BRCA1 Breast cancer 1 gene
BRCA2 BRCA2 gene
BRIP1 BRCA1-interacting protein 1
BUB1 Budding uninhibited by benzimidazoles 1
CAK CDK-activating kinase
CD Catalytic domain
CDK4 Cyclin-dependent kinase 4
CDKN2A Cyclin-dependent kinase inhibitor 2A
CETN2 Centrin, EF-hand protein 2
CHK1 Checkpoint, *Schizosaccharomyces pombe*, homolog of, 1
CIN Chromosomal instability
CLL Chronic lymphocytic leukemia
CMMR-D Constitutional mismatch repair deficiency
C-NHEJ Canonical NHEJ
CNVs Copy number variations
CPD Cyclobutane pyrimidine dimers
CRC Colorectal cancer
CSA Cockayne syndrome A
CSB Cockayne syndrome B
DBD DNA-binding domain
D-loop Displacement loop
DNA-PK DNA-dependent protein kinase
DNA-PKcs DNA-dependent protein kinase catalytic subunit
DOCK2 Dedicator of cytokinesis 2
dRP Deoxyribose phosphate
DSB Double-strand break
DSBR Double-strand break repair
EAC Esophageal adenocarcinoma
EGFR Epidermal growth factor receptor
ELMO1 Engulfment and cell motility gene 1
EPCAM Epithelial cellular adhesion molecule
EPHB2 Ephrin receptor EphB2
ER Estrogen receptor
ERCC1 Excision repair, complementing defective, in Chinese hamster, 1
EXO1 Exonuclease 1, *Saccharomyces cerevisiae*, homolog of
FA Fanconi anemia
FAAP100 Fanconi anemia–associated protein, 100-kD subunit
FAP Familial adenomatous polyposis
FAS FAS cell surface death receptor
FBXW7 F-box and WD-40 domain containing 7;
FEN1 Flap endonuclease 1
GG-NER Global genome NER
GRB1 Phosphatidylinositol 3-kinase-associated p85-alpha
HBOC Hereditary breast and ovarian cancer
HER2 Tyrosine kinase-type cell surface receptor HER2
HNPCC Hereditary nonpolyposis colon cancer
HNSCC Head and neck squamous cell carcinoma
HR Homologous recombination
IDLs Insertion/deletion loops
IR Irradiation
KLHL6 Kelch-like 6
KRAS V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

Ku70 Ku antigen, 70 kD subunit
Ku80 Ku antigen, 80 kD subunit
LFS Li–Fraumeni syndrome
LIG1 DNA ligase 1
LIG3 DNA ligase 3
LIG4 DNA ligase 4
LOH Loss of heterozygosity
MAD2 Mitotic arrest-deficient 2
MBD4 Methyl-CpG-binding domain protein 4
MDM2 Murine double minute 2
MEFs Embryonic fibroblasts
MLH1 MutL, *Escherichia coli*, homolog of, 1
MLH3 MutL, *Escherichia coli*, homolog of, 3
MMR Mismatch repair
MOS v-MOS Moloney murine sarcoma viral oncogene homolog
MRE11 Meiotic recombination 11, *Saccharomyces cerevisiae*, homolog of, A
MSH2 MutS, *Escherichia coli*, homolog of, 2
MSH3 MutS, *Escherichia coli*, homolog of, 3
MSH6 MutS, *Escherichia coli*, homolog of, 6
MSI Microsatellite instability
MSI-H High-frequency microsatellite instability
MutLα MLH1-PMS2 heterodimer
MutSα MSH2–MSH6 heteroduplex
MutSβ MSH2–MSH3 heteroduplex
MUTYH MutY, *Escherichia coli*, homolog of
MYD88 Myeloid differentiation primary response gene 88
NAD Nicotinamide adenine dinucleotide
Nbs1 Nibrin
NER Nucleotide excision repair
NF1 Neurofibromin 1
NHEJ Nonhomologous end joining
NOTCH1 NOTCH, *Drosophila*, homolog of, 1
OGG1 8-oxoguanine DNA glycosylase
8-oxoG 8-oxoguanine products
PADPr Poly(ADP) ribose
PALB2 Partner and localizer of BRCA2
PARG Poly(ADP-ribose) glycohydrolase
PARP1 Poly(ADP-ribose) polymerase 1
PARP2 Poly(ADP-ribose) polymerase 2
PCNA Proliferating-cell nuclear antigen
PIK3CA Phosphatidylinositol 3-kinase, catalytic, alpha
PIK3R1 Phosphatidylinositol 3-kinase, regulatory subunit 1
PMS1 Postmeiotic segregation increased, *S. cerevisiae*, 1
PMS2 Postmeiotic segregation increased, *S. Cerevisiae*, 2
PNKP Polynucleotide kinase 3′-phosphotase
Polβ DNA polymerase β
Polδ/ε DNA polymerase δ/ε
POLH Polymerase, DNA, eta
Polκ DNA polymerase κ
Polν DNA polymerase ν
6–4PP 6–4 photoproducts
PR Progesterone receptor
PRKDC Protein kinase, DNA-activated, catalytic subunit
PTCH Patched, *Drosophila*, homolog of
PTEN Phosphatase and tensin homolog
RAD23B RAD23 homolog B
RAD50 RAD50, *Saccharomyces cerevisiae*, homolog of
RAD51 RAD51, *S. cerevisiae*, homolog of
RAD54 RAD54, *S. cerevisiae*, homolog of

RAF Proto-oncogene RAF
RAS Oncogene RAS
RB1 RB1 gene
RFC Replication factor C
RNA PolII RNA polymerase II
ROS Reactive oxygen species
RPA Replication protein A
SAC Soluble adenylyl cyclase
SDSA Synthesis-dependent strand annealing
SHH Sonic hedgehog
SLX4 SLX4, *Saccharomyces cerevisiae*, homolog of
SMAD4 SMA- and MAD-related protein 4
SNP Single-nucleotide polymorphism
Sp1 Transcription factor Sp1
SPG20 SPG20 gene
SSB Single-strand break
SsDNA Single-stranded DNA
STAG2 Stromal antigen 2
STK12 Serine/threonine protein kinase 12
TCF4 Transcription factor 4
TC-NER Transcription-coupled NER
TFIIH Transcription initiation factor IIH
TGF-β Transforming growth factor, beta-1
TGFBR2 Transforming growth factor beta receptor 2
THBS1 Thrombospondin 1
TLR4 Toll-like receptor 4
TNKS TRF1-interacting, ankyrin-related ADP-ribose polymerase
TP53 Tumor protein p53
TRF1 Telomeric repeat-binding factor 1
USP7 Ubiquitin-specific processing protease 7
UV Ultraviolet
UV-DDB UV-damaged DNA-binding protein
UVSSA UV-stimulated scaffold protein A
WISP3 WNT1-inducible signaling pathway protein 3
WRN Werner syndrome ATP-dependent helicase
XLF XRCC4-like factor
XP Xeroderma pigmentosum
XPA XPA gene
XPB Xeroderma pigmentosum, complementation group B
XPC XPC gene
XPD XPD gene
XPE Xeroderma pigmentosum, complementation group E
XPF Xeroderma pigmentosum, complementation group F
XPG Xeroderma pigmentosum, complementation group G
XPO1 Exportin 1
XRCC1 X-ray repair, complementing defective, in Chinese hamster, 1
XRCC4 X-ray repair, complementing defective, in Chinese hamster, 4

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