

## Review Article

# Molecular Mechanisms of Ultraviolet Radiation-Induced DNA Damage and Repair

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DNA is one of the prime molecules, and its stability is of utmost importance for proper functioning and existence of all living systems. Genotoxic chemicals and radiations exert adverse effects on genome stability. Ultraviolet radiation (UVR) (mainly UV-B: 280–315 nm) is one of the powerful agents that can alter the normal state of life by inducing a variety of mutagenic and cytotoxic DNA lesions such as cyclobutane-pyrimidine dimers (CPDs), 6-4 photoproducts (6-4PPs), and their Dewar valence isomers as well as DNA strand breaks by interfering the genome integrity. To counteract these lesions, organisms have developed a number of highly conserved repair mechanisms such as photoreactivation, base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). Additionally, double-strand break repair (by homologous recombination and nonhomologous end joining), SOS response, cell-cycle checkpoints, and programmed cell death (apoptosis) are also operative in various organisms with the expense of specific gene products. This review deals with UV-induced alterations in DNA and its maintenance by various repair mechanisms.

## 1. Introduction

The stratospheric ozone layer is continuously depleting due to the release of atmospheric pollutants such as chlorofluorocarbons (CFCs), chlorocarbons (CCs), and organobromides (OBs). Consequently there is an increase in the incidence of UV radiation (UVR) on the Earth's surface [1] which is one of the most effective and carcinogenic exogenous agents that can interact with DNA and alter the genome integrity and may affect the normal life processes of all organisms ranging from prokaryotes to mammals [2–10]. However, wide variations in tolerance to UV-B among species and taxonomic groups have been reported. Moreover, ozone depletion followed by increased UV exposure has been predicted to continue throughout most of this century [11]. In all the groups of UVR (i.e., UV-A: 315–400 nm; UV-B: 280–315 nm; UV-C: <280 nm) UV-B radiation produces adverse effects on diverse habitats, even though most of the

extraterrestrial UV-B is absorbed by the stratospheric ozone [12]. UV-A radiation has a poor efficiency in inducing DNA damage, because it is not absorbed by native DNA. UV-A and visible light energy (up to 670–700 nm) are able to generate singlet oxygen (<sup>1</sup>O<sub>2</sub>) that can damage DNA via indirect photosensitizing reactions [13]. UV-C radiation is quantitatively absorbed by oxygen and ozone in the Earth's atmosphere, hence does not show much harmful effects on biota. Solar UV radiation is responsible for a wide range of biological effects including alteration in the structure of protein, DNA, and many other biologically important molecules, chronic depression of key physiological processes, and acute physiological stress leading to either reduction in growth and cell division, pigment bleaching, N<sub>2</sub> fixation, energy production, or photoinhibition of photosynthesis in several organisms [3, 9, 10]. It has been documented that UV-B severely affects survival, fecundity, and sex-ratio in several intertidal copepods [14]. One of the most prominent

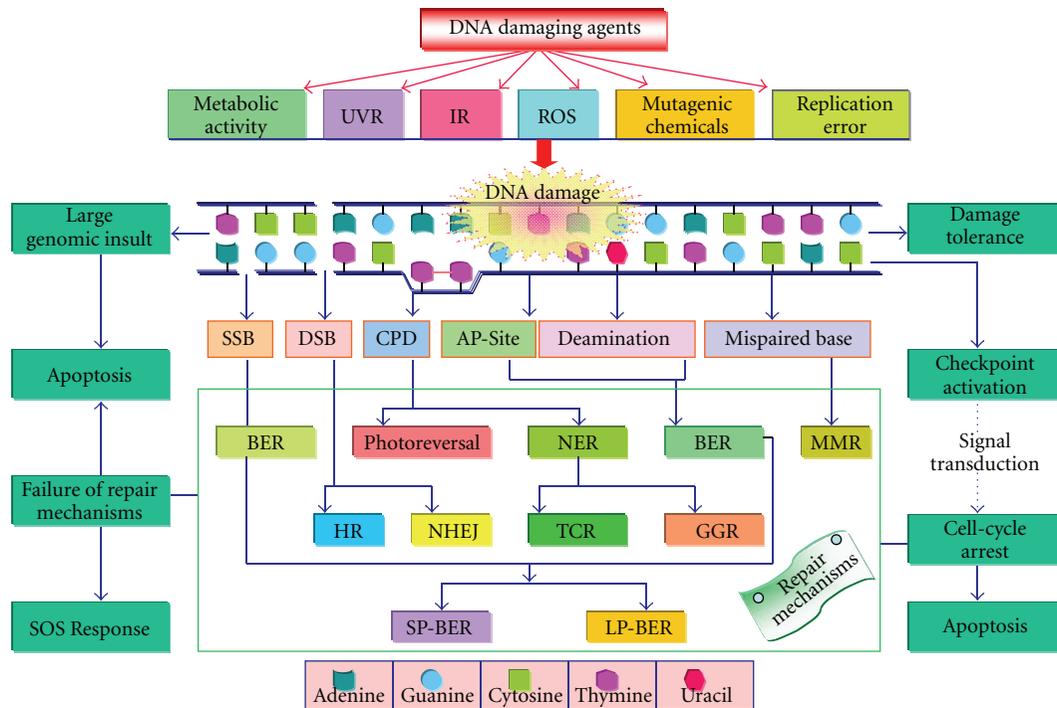


FIGURE 1: DNA damage and maintenance. Genomic lesions produced by various DNA damaging agents trigger several specific repair machinery to conserve the genomic integrity. In case of severe damage and/or failure of repair mechanisms, cells undergo apoptosis or induce a complex series of phenotypic changes, that is, SOS response. Sometimes the potentiality of lesions in the genome is mitigated by a phenomenon known as damage tolerance, during which DNA lesions are recognized by certain repair machinery, allowing the cells to undergo normal replication and gene expression. The cellular response to DNA damage may activate cell-cycle checkpoint by means of a network of signaling pathway that gives the cell extra time to repair the genomic lesions or may induce cell suicide response/programmed cell death (PCD).

targets of solar UV-radiation is cellular DNA, which absorbs UV-B radiation and causes adverse effects on living systems such as bacteria [15, 16], cyanobacteria [17], phytoplankton [18], macroalgae [19], plants [20], animals, and humans [21–23].

Although UV-B radiation has less than 1% of total solar energy, it is a highly active component of the solar radiation that brings about chemical modification in DNA and changes its molecular structure by the formation of dimers. Certain UV-absorbing pigments are produced by a number of organisms as a first line of defense; however, they are unable to avoid UV-radiation completely from reaching DNA in superficial tissue [28–32]. Certain enzymes, such as superoxide dismutase (SOD), catalase (CAT), peroxidase (POD), and scavengers such as vitamin C, B, and E, cysteine, and glutathione play an additional role in defense against UV radiation [33]. However, as a second line of defense several organisms have developed a number of specific and highly conserved repair mechanisms such as photoreactivation, excision repair, mismatch repair (MMR), double strand break (DSB) repair and certain other mechanisms like damage tolerance (dimer bypass), SOS (save our soul) response, checkpoint activation, and programmed cell death (PCD) or apoptosis (Figure 1) that efficiently remove DNA lesions ensuring the genomic integrity [22]. Plants are unique in the obligatory nature of their exposure

to UVR; it is also conceivable that they may also have evolved certain efficient repair mechanisms for the elimination of UV-induced DNA damage. However, a number of questions concerning the basic phenomena of the DNA repair in plants remain to be elucidated. In the following, we discuss the molecular mechanisms of UV-induced DNA damage and repair mechanism (s) operative in various organisms.

## 2. UV-Induced DNA Damage

Induction of DNA damage by solar UVR is a key event that drastically influences the normal life processes of all organisms. A number of endogenous factors such as free radicals [34] generated during metabolic processes as well as exogenous factors such as UV or ionizing radiations [35] are known to interfere with genome integrity. DNA damage results in (i) misincorporation of bases during replication process, (ii) hydrolytic damage, which results in deamination of bases, depurination, and depyrimidination [36], (iii) oxidative damage, caused by direct interaction of ionizing radiations (IR) with the DNA molecules, as well as mediated by UV radiation-induced free radicals or reactive oxygen species [37, 38], and (iv) alkylating agents that may result in modified bases [36, 39]. The hydrolytic deamination (loss of an amino group) can directly convert

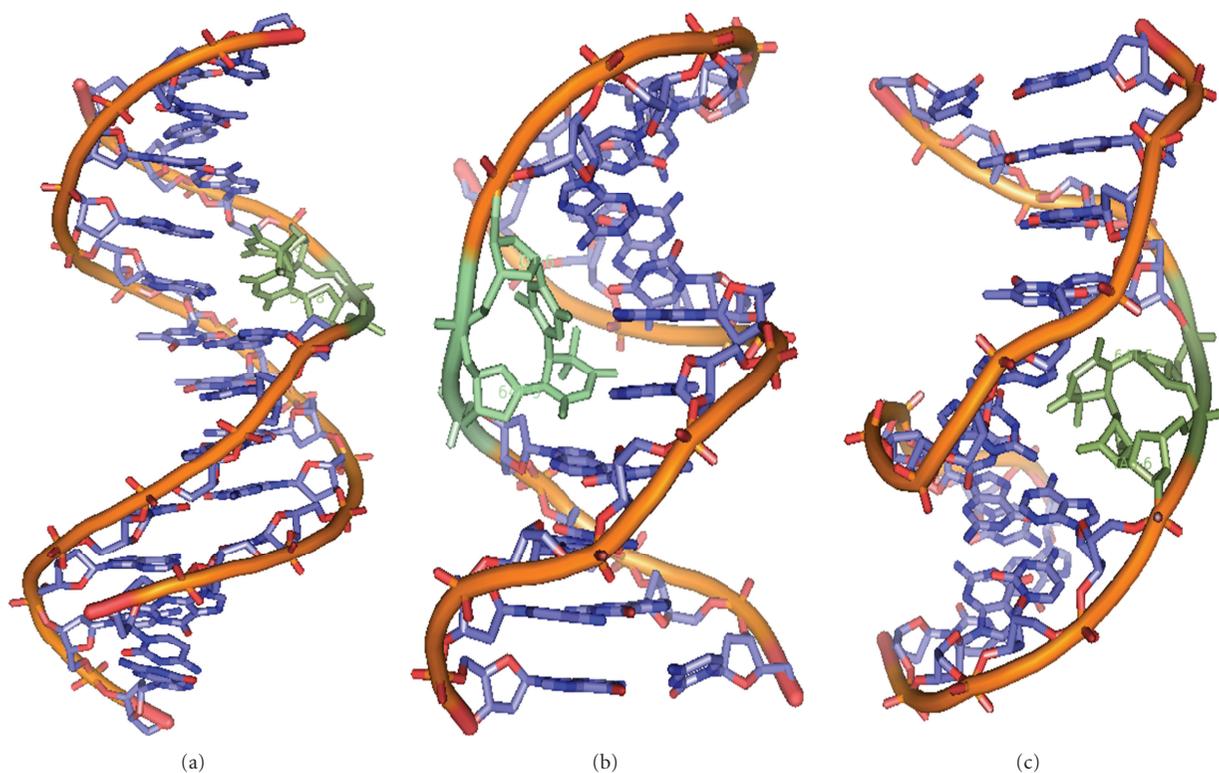


FIGURE 2: Structures of DNA duplexes showing the presence of lesions (in green) such as CPD (a), 6-4PP (b), and 6-4 Dewar dimer (c). Hydrogen atoms are not shown, prepared from PDB entries 1TTD [24], 1CFL [25], and 1QKG [26] using PyMol. (version 1.1r1) [27].

one base to another; for example, deamination of cytosine results in uracil and at much lower frequency adenine to hypoxanthine. In depurination/depyrimidination, there are complete removals of purine/pyrimidine bases, leaving the deoxyribose sugar depurinated/depyrimidinated, that may cause breakage in the DNA backbone. The exposure of UVR, IR, and certain genotoxic chemicals may result in single as well as double DNA strand breaks. Among different types of damages, DNA double strand breaks (DSBs) are the most deleterious, since they affect both strands of DNA and can lead to the loss of genetic material. At high concentrations oxygen-free radicals or, more frequently, reactive oxygen species (ROS) can induce damage to cell structure, lipids, proteins as well as DNA and results in oxidative stress which has been implicated in a number of human diseases [40]. The hydroxyl radicals ( $\text{OH}^\bullet$ ) can damage all components of DNA molecules such as purine and pyrimidine bases and also the deoxyribose backbone, inhibiting the normal functions of the cell [37, 38].

### 3. UV-Induced Pyrimidine Photoproducts

UV-B radiation is one of the most important energetic solar components that may lead to the formation of three major classes of DNA lesions, such as cyclobutane pyrimidine dimers (CPDs), pyrimidine 6-4 pyrimidone photoproducts (6-4PPs), and their Dewar isomers (Figure 2) [5, 22, 23, 41–43]. CPDs correspond to the formation of a four-member

ring structure involving C5 and C6 of both neighboring bases whereas 6-4PPs are formed by a noncyclic bond between C6 (of the 5'-end) and C4 (of the 3'-end) of the involved pyrimidines via spontaneous rearrangement of the oxetane (when the 3'-end is thymine) (Figure 3(a)) or azetidone (when the 3'-end is cytosine) (Figure 3(b)) intermediates [5, 44]. The 6-4PPs are eagerly converted into their Dewar valence isomers upon exposure to UV-B or UV-A radiation that may further undergo reversion to the 6-4PPs upon exposure to short-wavelength UV radiation [45]. Two adjacent cytosines are considered as mutation hotspots of UVB and UVC radiations [42]. It has been found that T-T and T-C sequences are more photoreactive than C-T and C-C sequences [46]. The diastereoisomers of pyrimidine dimers (Figure 4) can be observed in free solution that differ in the orientation of the two pyrimidine rings relative to the cyclobutane ring, and on the relative orientations of the C5–C6 bonds in each pyrimidine base [44]. It has been demonstrated that the main photoproducts are *cis-syn*-configured CPD lesions, while *trans-syn*-configured CPD lesions are formed in much less quantity [47]. In double stranded B-DNA, where the dimer entails two adjoining pyrimidine bases on the same DNA strand, only the *syn* isomers can be generated, whereas the *cis* isomer is preferred over the *trans* isomer to a great extent [42]. The incidence of *trans-syn* isomer in single-stranded or denatured DNA is more common because of the increased flexibility of the DNA backbone. A few CPD lesions (i.e., *cis-syn* or *trans-anti* isomers) can also be detected in aqueous

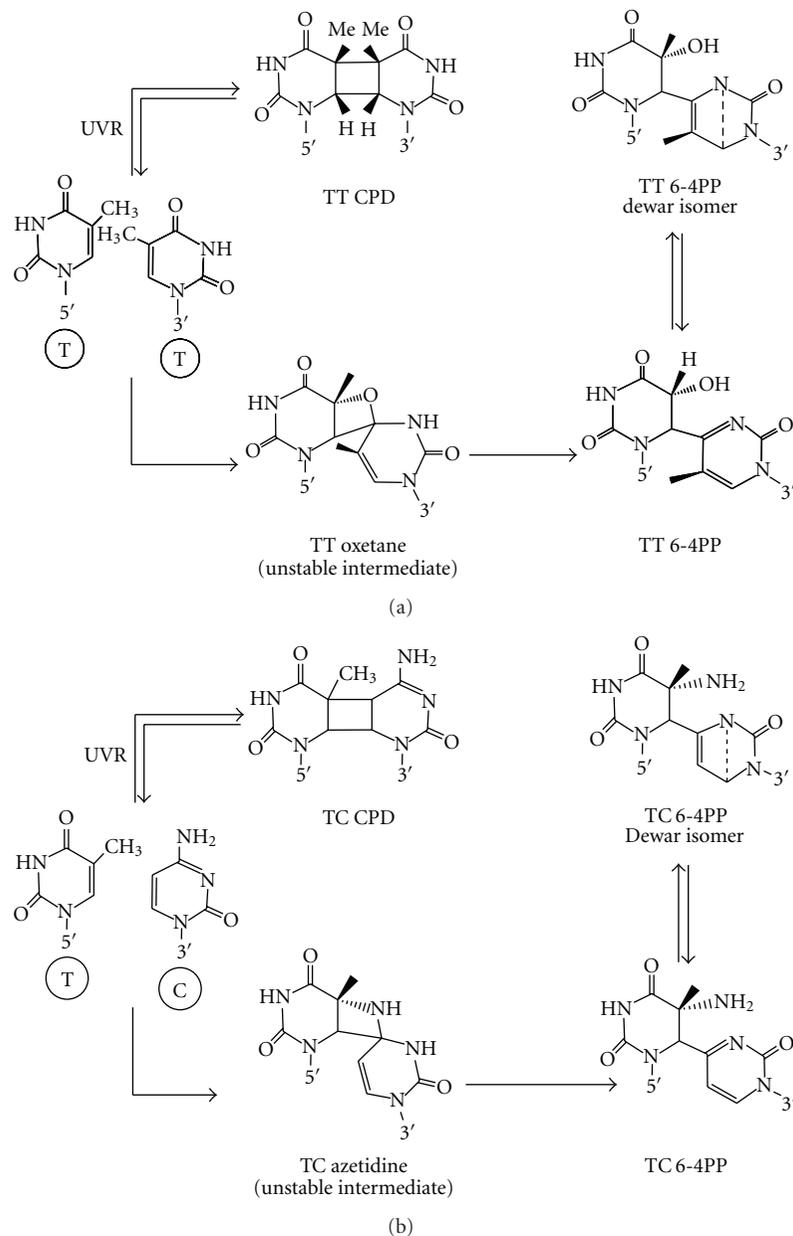


FIGURE 3: Pathway of UVR-induced T-T (a) and T-C (b) CPD, 6-4PPs, and their Dewar isomers.

solutions by UV-C irradiation [48]. The formation of “spore photoproduct” has been detected in UV-irradiated bacterial spores by the addition of methyl group of one thymine residue to the C5 position of an adjacent thymine. In most cellular environments, there is no much significance of this photoproduct, since it requires anhydrous conditions for its formation [49].

The base damage by UVR is determined by the flexibility of the DNA strand as well as nature and position of the base. CPDs are formed at higher quantity by cycloaddition reaction between two pyrimidine bases [47] in single-stranded DNA (ssDNA) and at the flexible ends of poly (dA)-(dT) tracts, but not at their rigid centre [50, 51]. Bending of DNA towards the minor groove reduces CPDs

formation [52]. One of the transcription factors, TATA-box binding protein (TBP), promotes the selective formation of 6-4PPs in the TATA-box, where the DNA is bent, but CPDs are formed preferentially at the edge of the TATA box and outside where the DNA is not bent [53]. The amounts of CPDs and 6-4PPs are about 75 and 25%, respectively, of the total UV-mediated DNA damage products [22]; however, the ratio between the yield of CPDs and 6-4PPs mainly depends upon the two adjacent bases involved in the formation of dimers [54]. Thus the heterogeneous distribution of the UV-induced photolesions in the DNA depends on the sequences that facilitate DNA bending as well as the chromatin modulation through the binding of specific protein [55]. Mapping of CPDs in the nucleosome core

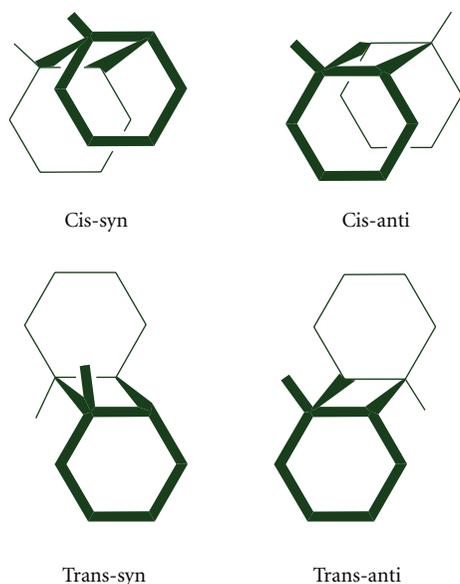


FIGURE 4: Possible diastereoisomers of pyrimidine T  $\diamond$  T dimer.

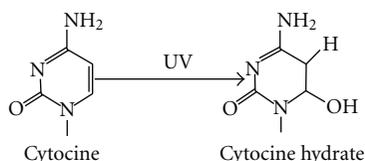


FIGURE 5: Formation of cytosine photohydrate (6-hydroxy-5,6-dihydrocytosine) as a result of photohydration reaction.

regions of UV-treated chromatin has revealed the formation of CPDs with an average distance of 10.3 bases, away from the surface of histones [56]. The formation of photoproducts is not restricted to cells exposed to UV-B or UV-B + UV-A radiations; UV-A-induced formation of CPDs has also been observed in bacteria as well as in eukaryotic cells and whole skin [57–59]. Recent studies on the effects of UV-A radiation on rodent and human skin cells have revealed that CPDs are in larger yields than 8-oxo-7,8-dihydroguanine (the most frequent UVA-induced DNA lesion) and DNA strand breaks [48, 60]. The occurrence of 5-methylcytosine-containing photoproducts in UV-irradiated DNA is still controversial. However, Su et al. [61] have reported a new photoproduct of 5-Methylcytosine and Adenine characterized by high-performance liquid chromatography and mass spectrometry. An additional photochemical characteristic for cytosine is the formation of monomeric pyrimidine photoproduct “cytosine photohydrate” (6-hydroxy-5,6-dihydrocytosine) as a result of photohydration reaction (Figure 5) [62]. There is little information concerning the formation of cytosine hydrates in UV-irradiated DNA due to instability of the resulting photoproduct [63]. The oxidation product of pyrimidine bases such as pyrimidine glycols is also formed by means of hydration reaction [42].

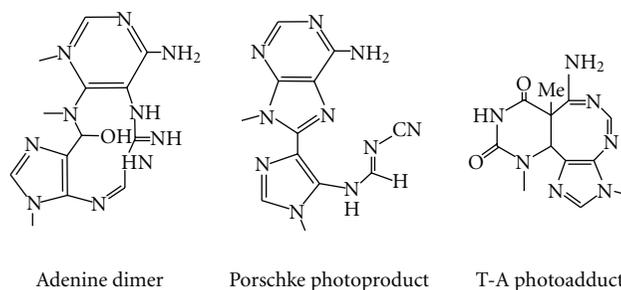


FIGURE 6: Structure of purinic photoproduct, that is, adenine dimer, porschke photoproduct and thymine-adenine photoadduct.

#### 4. UV-Induced Purine Photoproducts

Although dipyrimidine photoproducts are the preferential outcome of UV-B radiation, the biological importance of UV radiation-induced modifications of DNA purine bases has also been recognized [64]. These comprise the photoproducts that involve, at least, one adenine residue that undergoes photocycloaddition reactions with contiguous adenine or thymine (Figure 6) upon exposure to UV-B radiation [65, 66]. The extent of adenine-containing photoproduct (A-T) is very low ( $1 \times 10^{-5}$  in native DNA) but these lesions may contribute to the biological effects of UV radiation in view of the fact that the A-T adduct has been shown to be mutagenic [67, 68]. Photodimerization of adenine (A) involves the cycloaddition of N7-C8 double bond of the 5'-A across the C6 and C5 positions of the 3'-A [65, 69] and generates a very unstable azetidine intermediate. This intermediate photoproduct undergoes competing reaction pathways to form two distinct adenine photoproducts such as adenine dimer (A=A) and Porschke photoproduct (Figure 6) [70]. Conversion of both these photoproducts into 4,6-diamino-5-guanidinopyrimidine (DGPY) and 8-(5-aminoimidazol-4-yl)adenine (8-AIA), respectively, can be detected from individual acid hydrolysates of UV-irradiated polynucleotides and DNA [71]. It has been found that complexing of UV-irradiated poly(dA)-poly(dT) effectively reduces the formation of A=A photoproduct [71]. Moreover, photoreactivity of adjoining adenine bases in DNA is strongly suppressed by the complementary base pairing [50, 72]. UV-induced ROS acts as a powerful oxidant that may cause oxidative DNA damage. A number of oxidation products of purine bases such as 8-oxo-7,8-dihydroguanyl (8-oxoGua), 8-oxo-Ade, 2,6-diamino-4-hydroxy-5-formamidoguanine (FapyGua), FapyAde, and oxazolone have been reported to form upon exposure of DNA to UV radiation [44, 73, 74].

Overall, it has been concluded that UV-induced DNA lesions such as CPDs, 6-4PPs, abasic site, strand breaks, and oxidative product are the predominant and most persistent lesions and if not repaired may cause severe structural distortions in the DNA molecule, thereby affecting the important cellular processes such as DNA replication and transcription, compromising cellular viability and functional integrity and ultimately leading to mutagenesis, tumorigenesis, and cell death [30, 36].

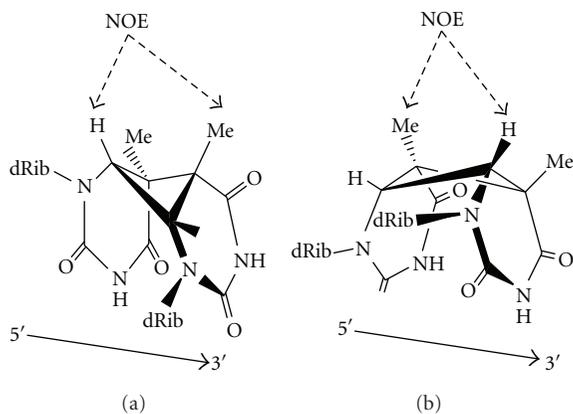


FIGURE 7: *Cis-syn* CPD showing the right-handed or left-handed twist in DNA duplex. Dotted arrows elucidate the strongest nuclear overhauser enhancement (NOE) interaction in both cases (Adopted from Lukin and de los Santos [75]).

## 5. Differential Effects of CPDs and 6-4PPs on DNA Conformation

UV-induced DNA lesions such as CPDs and 6-4PPs show differential effects on DNA conformation, impairing their regulatory functions and other dynamic processes [24, 26, 75, 76]. Nuclear Magnetic Resonance (NMR) spectroscopy has presented new insights on UV radiation-induced nucleic acid conformation. It has been well established that the comparative orientation of damaged residues is unusual from that observed in unmodified DNA duplexes [75]. Nuclear overhauser enhancement (NOE) study of interactions among the photoadduct H6 and methyl ( $\text{CH}_3$ ) groups has established that the *cis-syn* CPD changes the cyclobutane conformation from a left-handed twist (observed in the isolated dimer) to a right-handed twist in DNA duplex [46] (Figure 7). Assessment of the chemical shift data suggests that the DNA helix is disturbed more along the 3'- and 5'-side of the *cis-syn* and *trans-syn* dimer, respectively. It was revealed that the presence of *trans-syn* CPD causes distortion to a great extent than the *cis-syn* product by means of a kink or dislocation at the 5'-side of the dimer in double-stranded DNA [77]. NMR and X-ray diffraction studies of the ultraviolet photoproduct, *cis-syn* CPD, with the S-cyanoethyl phosphotriester have revealed that the two pyrimidine bases are rotated by  $-29^\circ$  base twist, contrasting to the right-handed  $36^\circ$  value observed in B-form DNA [78, 79]. Moreover, in contrast to the *cis-syn* CPD, the duplex spectra of the *trans-syn* lesion illustrated no abnormally shifted  $^{31}\text{P}$  or imino proton signal, signifying the absence of major distortions in the conformation of the sugar-phosphate backbone [75]. The thymine (T) residues of the CPD form stable wobble pairs with the opposite guanine (G) residues. The T6-G15 wobble pair of the CPD formed hydrogen bonds between the T6-imino and G15-O6 and between the G15-imino and T6-O2. The two T (T5, T6) residues of the CPD in the CPD/GG duplex form wobble

base pairs with the opposite G residues, similar to the T6-G15 base pair in the CPD/GA duplex [80]. It has been reported that the preexisting CPDs in the DNA molecule can influence its rotational setting on the histone surface during nucleosome formation [81]. Recently, Rumora et al. [82] have examined the thymine dimer-induced structural changes to the DNA duplex with several small, base-selective reactive chemical probes. The formation of 6-4PPs and their Dewar isomers cause remarkable change in the conformation of DNA duplex. The one- and two-dimensional NMR data on the (6-4)-adduct-containing DNA duplex decamer was analyzed in  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  solutions to elicit the base pairing and unusual conformation in the vicinity of the lesion [76, 83, 84]. The distortion of the double helix caused by the 6-4PP is much greater than that of the CPD [85].

The main conformational perturbations caused by the (6-4) adduct and Dewar product are concerned with their effects on global DNA curvature. Both duplex decamers are significantly bent at the lesion sites. In contrast to the 6-4PPs, the 5,6-dihydro-5-hydroxythymine base is the most perturbed part of the 6-4 Dewar lesion. Even though there are no hydrogen bonds between 5,6-dihydro-5-hydroxythymine and its partner adenine residue, this lesion produces minor distortions in comparison to the 6-4PP. In general helical bending induced by the (6-4) adducts and the Dewar product is  $44^\circ$  and  $21^\circ$ , respectively [76]. All the supplementary imino proton resonances from the flanking base pairs were observed in the hydrogen-bonded region, which indicate that the structure of the (6-4) adduct inside the duplex shows a distinctive base orientation due to (6-4) covalent linkage which makes a normal Watson-Crick-type hydrogen bonding unfavorable at the 3'-side of the lesion site with an empty space between the 3'-thymine (T6) and its opposite base (A15) [76]. Contrary to the duplex (6-4) decamer which retains a hydrogen-bonded imino proton at the 5'-side (T5) of the (6-4) lesion, the T5 imino proton of the Dewar lesion is not hydrogen-bonded. The NMR characterization of a 6-4PP dimer containing duplex showed that the 5'-residue of the lesion remains essentially unperturbed. However, the 5'-pyrimidine residue loses aromaticity and acquires an additional hydrophilic group [75, 83]. The glycosyl bond torsion angle at the T5 residue of the (6-4) lesion and the Dewar lesion prevails in the anti and high-anti conformation, respectively, and thus both the lesions exhibit considerable differential effects on DNA backbone conformation. It has been observed that the large structural distortion induced by the (6-4) lesion may ensure a favorable recognition by the repair enzyme, which may possibly elucidate the correlation with the elevated repair rate of the T-T (6-4) adduct than of the T-T Dewar product and the T-T *cis-syn* dimer [76].

## 6. UV-Induced DNA Double Strand Breaks

The generation of DNA double strand breaks (DSBs) in UV-irradiated cells, specifically in replicating DNA, has been known for a long time [86]. DNA strand breaks are observed extensively in cells under UV-B irradiation [87, 88]. UV-B-induced ROS [89] as well as DNA lesions

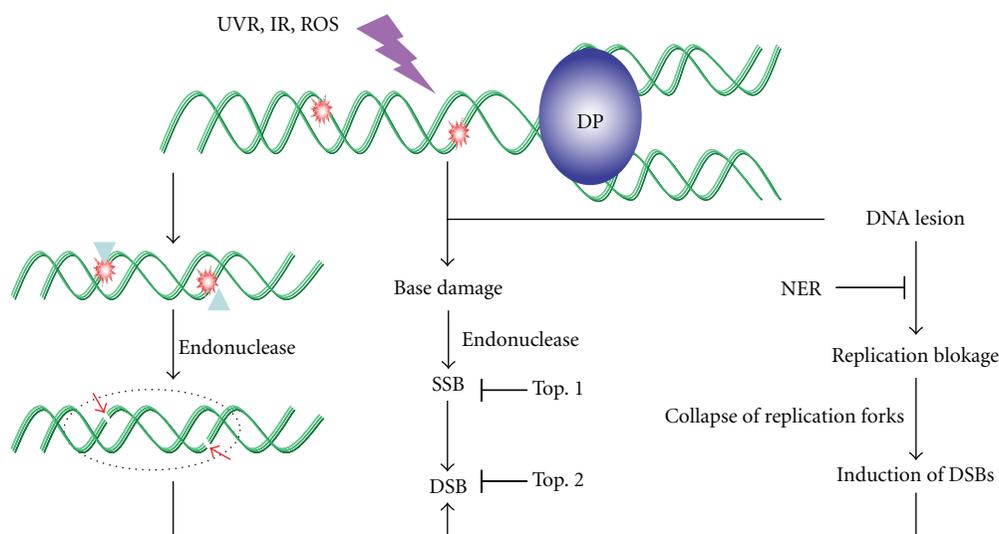


FIGURE 8: Schematic representation showing different pathways of DSBs.

(CPDs and 6-4PPs) may cause primary as well as secondary breaks, respectively. These lesions are commonly associated with transcription/replication blockage that may lead to production of DNA double-strand breaks (DSBs) at the sites of collapsed replication forks of CPDs-containing DNA [90, 91] (Figure 8). Dunkern and Kaina [92] also observed UV-C-induced DNA DSBs, arising from replication of damaged DNA. A significantly low amount of DSBs was found in the cell where replication was inhibited. It was assumed that initial photoproducts are converted into DSBs during DNA replication, due to not a distinct process, that is, “collapse of replication forks” [93]. After labeling of replicating DNA of UV-irradiated SV40-transformed human cell lines with radioactive precursors, an increased number of DSBs was observed in NER deficient cells in comparison to NER proficient cells. These results further support the view that DSBs are produced during the replication of unrepaired UV-induced DNA lesions [91]. DSBs can be formed in response to the repair of single strand breaks (SSBs) passing through base excision repair (BER) [94, 95]. Overall, it seems that UV radiation does not directly produce DNA DSBs but rather produces pyrimidine dimers and other photoproducts leading to replication arrest and DSBs. UV-induced replication arrest in the xeroderma pigmentosum variant (XPV) followed by the accumulation of Mre11/Rad50/Nbs1 complex and phosphorylated histone H2AX ( $\gamma$ -H2AX) in large nuclear foci at sites of stalled replication forks also suggests that UV damage leads to the formation of DSBs during the course of replication arrest [90, 95].

A number of pathways have been considered for the formation of DSBs at a stalled replication fork. It was shown that when the DNA replication machinery encounters a replication-blocking lesion, DNA polymerase (DP) enzyme is stalled at the blocked site resulting in the formation of a Y-shaped DNA structure, which may be recognized by a specific endonuclease, that successively makes a nick in the template strand resulting in the induction of a DSB close to the

replication-blocking lesion [144]. Furthermore, replication stresses may trap topoisomerase I (Top1) cleavage complexes leading to generation of DSBs by preventing Top1-mediated DNA religation [145]. Free radicals may also cause DSBs [146] by preventing the topoisomerase II (Top2)-mediated DNA religation [144, 147]. Recently, Harper et al. [148] have shown that radiation-induced SSBs and non-DSB DNA damage contribute to the formation of replication-induced DSBs. In spite of the above possible facts regarding the formation of DSBs, more experimental evidences are still needed.

## 7. Detection of DNA Damage

Several workers have attempted to detect different types of DNA lesions and presently a number of detection strategies are widely used (Table 1). An alkaline gel method for quantitating single-strand breaks (SSBs) in nanogram quantities of nonradioactive DNA was developed by Freeman et al. [149]. Mitchell et al. [150] have developed a method for the detection of CPDs, where DNA is labeled with radioactive substances followed by agarose gel electrophoresis and densitometric analysis and finally digesting with endo. III and endo.V before analyzing on sequencing gels. UV-B induced DNA damage in mammalian genome was reported by Wang et al. [96] using the PCR-based short interspersed DNA element- (SINE-) mediated detection method. For analyzing the 6-4PPs, terminal transferase-dependent PCR (TD-PCR) has been used [97]. UV-induced decrease in template activity of genomic DNA of cyanobacterium *Anabaena* strain BT2 was documented by Kumar et al. [98] using the PCR-based assays such as random amplified polymorphic DNA (RAPD) and rDNA amplification. Similarly, UV-B-induced DNA damage was also detected in *Anabaena variabilis* PCC 7937 and *Rivularia* sp. HKAR-4 by PCR (data not published). The formation of thymine dimer ( $T^{\wedge}T$ ) within

TABLE 1: Various strategies for the detection of damaged DNA.

DNA damage detection strategies	Types of lesions detected	References
PCR based assay (TDPCR, LMPCR, ICPCR, SINE)	Decrease in DNA template activity, T $\leftrightarrow$ T CPDs, 6-4PPs	[96–99]
Commet assay (Single-cell gel Electrophoresis)	Oxidative DNA damage and single/double strand break	[100, 101]
Halo assay/AHA/FHA	Chromatin fragility/single strand breaks at the single cell level	[102, 103]
TUNEL assay	Single/double strand breaks, apoptosis	[104, 105]
HPLC-MS/MS	Oxidative DNA damage; CPDs, 6-4PPs and their related Dewar valence isomers; 5-hydroxy-2-deoxyuridine, 8-oxo-7,8-dihydro-2-Deoxyadenosine; 5-Methylcytosine and adenine	[48, 54, 61, 106]
FISH	Chromosomes with numerical aberrations	[107, 108]
FCM	Chromosomal aberrations, sister chromatid exchange, chemical adducts to DNA and DNA strand breakage	[109, 110]
Annexin V labeling	Chromatin condensation, DNA fragmentation, radiation-induced apoptosis	[109, 111]
Immuno-dot-blot assay	CPDs, 6-4PPs and their Dewar valence isomers	[17, 59, 112, 113]
RIA	CPDs and 6-4PPs	[114, 115]
GC-MS	Strand break, modified bases, abasic sites, DNA-protein crosslinks and other oxidative DNA damage.	[39]
FADU	Single/double strand breaks and alkali-labile sites	[88, 116]
NMR spectroscopy	Lesions induced distortions of DNA duplex	[78–80]

PCR: polymerase chain reaction; TDPCR: terminal transferase dependent PCR; LMPCR: ligation-mediated PCR; ICPCR: immuno-coupled PCR; SINE: short interspersed DNA element; AHA: alkaline-halo assay; FHA: fast halo assay; TUNEL: terminal deoxyribonucleotidyl transferase mediated deoxyuridine triphosphate nick end labeling; HPLC-MS/MS: high-performance liquid chromatography coupled to tandem mass spectrometry; FISH: fluorescence *in situ* hybridization; FCM: flow cytometry; RIA: radio immunoassay; ELISA: enzyme-linked immunosorbent assay; GC-MS: gas chromatography-mass spectrometry; NMR: nuclear magnetic resonance spectroscopy.

human genomic DNA has been detected by immunocoupled PCR (IC-PCR) [99]. DNA damage such as SSBs, DSBs, and oxidative DNA damage caused by UVR, ultrasound electromagnetic frequency radiation, and so forth may be detected by comet assay [100]. Recently, a modified version of comet assay (apo/necro-comet assay) has been developed that differentiates viable, apoptotic, and necrotic cells and also correlates the DNA fragmentation pattern [101]. Both single and DSBs as well as apoptosis can also be detected by TUNEL assay [104, 105]. However, it has been experienced that TUNEL assay is not able to distinguish various types of cell death; hence, an alternate method based on flow cytometry (FCM) has been developed for the detection of apoptosis [109]. Recently, apoptosis in tumor cells caused by X-rays has been analyzed using  $^{125}\text{I}$ -labeled annexin V [111]. FCM assay is useful in detecting chromosomal aberrations, sister chromatid exchange, chemical adducts to DNA, and DNA strand breakage [110]. Alkaline unwinding FCM (AU-FCM) may be used to detect nucleotide excision repair (NER) [151]. The changes in DNA organization in the individual cells can be determined by halo assay [102]. SSBs at the single cell level can be assessed by alkaline-halo assay (AHA), where cells are embedded in melted agarose and spread on the microscope slide and then incubated in a high-salt alkaline lysis solution followed by another incubation in a hypotonic alkaline solution and, finally, stained with ethidium bromide (EtBr). Under

these conditions, single-stranded DNA fragments diffuse radically from the nuclear cage [103]. DNA strand breaks (SSBs, DSBs, and alkali-labile sites) induced by genotoxic agent such as UVR can also be detected by fluorometric analysis of DNA unwinding (FADU) assay, which was first reported by Birnboim and Jevcak [116] to detect X-ray-induced DNA damage in mammalian cells. Numerical aberrations in chromosome can be detected efficiently by fluorescence *in situ* hybridization (FISH) method [107]. Recently, immuno-dot-blot assay is used extensively to detect UV-induced photoproducts in various organisms such as mammals, cyanobacteria, phytoplankton, macroalgae, and liverwort [17, 59, 112, 113]. This technique is based on use of thymine-dimer specific antibodies followed by blotting and chemiluminescence method. Another detection strategy includes radio-immunoassay (RIA) which is used to estimate CPDs and 6-4PPs [114]. The very low amount of CPDs caused by UVR in bacterioplankton and marine viruses may be detected very efficiently using RIA method [115]. Kara et al. [152] have studied the electrochemical detection of DNA damage by direct and indirect irradiation with radioactive technetium (TC-99m) and iodine (I-131). Certain photoproducts such as 5-Methylcytosine and adenine can be detected by high-performance liquid chromatography and mass spectrometry [61]. Recently, Kumari et al. [108] have made an attempt to dissect various strategies for detection of DNA lesions produced by a number of genotoxic agents.

TABLE 2: Photolyase enzymes in four different kingdoms.

Kingdom	Organism	CPD Photolyase	6-4PP Photolyase	References
Archaeobacteria	<i>Halobacterium halobium</i>	+	–	[117]
	<i>Methanobacterium thermoautotrophicum</i>	+	–	[118, 119]
	<i>Sulfolobus tokodaii</i>	+	–	[120]
Eubacteria	<i>Bacillus firmus</i>	+	–	[121]
	<i>Escherichia coli</i>	+	–	[122, 123]
	<i>Salmonella typhimurium</i>	+	–	[122]
	<i>Anacystis nidulans</i>	+	–	[124]
	<i>Synechocystis sp. PCC 6803</i>	+	–	[125]
	<i>Streptomyces griseus</i>	+	–	[126]
	<i>Myxococcus xanthus</i>	+	–	[127]
	<i>Vibrio cholerae</i>	+	–	[128]
Eukaryotes	<i>Saccharomyces cerevisiae</i>	+	–	[122]
	<i>Neurospora crassa</i>	+	–	[129, 130]
	<i>Drosophila melanogaster</i>	+	+	[131]
	<i>Homo sapiens</i>	?	?	[118, 132]
	<i>Carassius auratus</i>	+	–	[133]
	<i>Oryzias latipes</i>	+	–	[118]
	<i>Monodelphis domestica</i>	+	–	[134]
	<i>Potorous tridactylis</i>	+	–	[118]
	<i>Xenopus laevis</i>	+	+	[135]
	<i>Arabidopsis thaliana</i>	+	+	[136]
	<i>Chlamydomonas reinhardtii</i>	+	–	[137]
	<i>Cucumis sativus</i>	+	–	[138, 139]
	<i>Ginkgo biloba</i>	+	–	[140]
<i>Medicago sativa</i>	+	–	[20]	
<i>Triticum sp.</i>	+	–	[141]	
Viruses	<i>Fowl pox virus</i> (FPV)	+	–	[142]
	<i>Melanoplus sanguinipes</i> entomopox virus (MsEPV)	+	–	[143]
	<i>Chrysodeixis chalcites</i> nucleopolyhedrovirus (ChchNPV)	+	–	[106]

## 8. DNA Repair

The idea about the ability of living beings to overcome the lethal effects of UV-radiation emerged as early as the mid 1930s [153], but the existence of repair mechanisms was observed by Kelner [154] and Dulbecco [155] independently. The determination of a particular repair pathway within the cell mainly depends on the types and location of lesions in the genome [156]. The biochemical and molecular studies on repair pathways have been extensively investigated in some model organisms such as *E. coli*, *S. cerevisiae*, and human, where specialized repair proteins scan the genome continuously and encounter the DNA lesions by triggering several distinct repair mechanisms such as photoreactivation, excision repair (BER and NER), mismatch repair (MMR), and some specialized forms of repair system such as SOS response, damage tolerance, and apoptosis.

## 9. Photoreactivation

The process of photoreactivation is executed by means of a photoreactivating enzyme known as “photolyase”, which is well conserved and found throughout the three domains of life (Table 2). The enzyme binds specifically to the CPDs (CPD photolyase) or 6-4PPs (6-4 photolyase) and directly monomerizes the cyclobutane ring of the pyr > pyr, using the energy of visible/blue-light and protects the genome from deleterious effects of UVR [157, 158]. The absorption of every blue-light photon may split approximately one dimer [159]. CPD photolyases have been reported in diverse groups such as archaea, bacteria, fungi, virus, plants, invertebrates, and many vertebrates including aplacental mammals (Table 2). On the other hand, 6-4 photolyases have been identified in certain organisms like *Drosophila*, silkworm, *Xenopus laevis*, and rattle snakes [22]. Photolyases seem to be

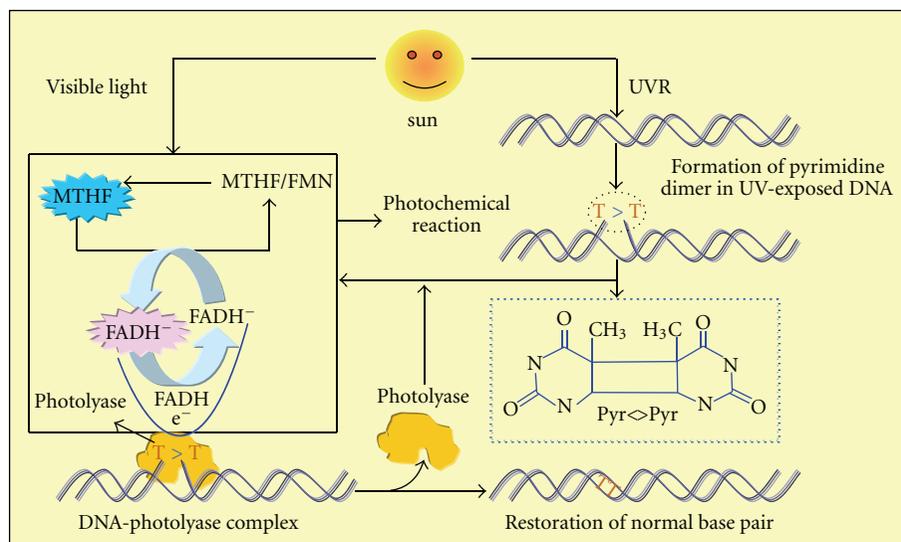


FIGURE 9: Photoreactivation: incidence of ultraviolet radiation (UVR) results in pyrimidine lesion (thymine dimer), which is recognized by a photoreactivating enzyme “photolyase”. The light energy (>380 nm) is trapped by the antenna molecules of photolyase (such as MTHF/8-HDF/FMN) and transfers them to catalytic cofactor FADH<sup>-</sup> which becomes excited and transfers energy to the pyrimidine dimer in the form of e<sup>-</sup>, splitting the CPD into two monomeric unit, and then electron is transferred back to the flavin molecule.

absent or nonfunctional in placental mammals like human [118, 132, 160]. However, Sutherland [161], Sutherland and Bennett [162], and Harm [163] have demonstrated photolyase activity in cells and tissues, including white blood cells (WBCs) of several placental mammals, such as humans, ox, cat, and mouse. A number of workers have identified a human photolyase which shows homology with *Cry* gene (plant blue-light receptor) and about 40% sequence identity to the *Drosophila* 6-4 photolyase, but their exact roles in repair process, whether it acts as a photolyase or as a photoreceptors, are still under investigation [164].

DNA photolyases (45–66 kDa) having 420–616 amino acid residues [158] are monomeric flavin-dependent repair enzymes, consisting of two known cofactors, a catalytic cofactor and a light-harvesting cofactor. Till date, 5,10-methenyltetrahydrofolate (MTHF) [122], 8-hydroxy-5-deaza-riboflavin (8-HDF) [124], and FMN [165] are known as light-harvesting cofactors, which absorb light energy efficiently and transfer them to FADH<sup>-</sup> [166]. Deprotonated reduced flavin adenine dinucleotide (FADH<sup>-</sup>) is found in all known photolyases as a catalytic cofactor, which transfers energy in the form of an electron to the CPD, splitting the cyclobutane ring with the generation of two monomeric bases [157, 167] (Figure 9).

In comparison to other eukaryotic systems, reports on the repair of UV-induced DNA damage in plants are still very limited. To avoid the deleterious effects of UVR, plants have acquired two main protective strategies; shielding by flavonoids and phenolic compounds [168, 169] and DNA repair by photoreactivation. Photoreactivation mediated by the enzyme photolyases is thought to be the major DNA repair pathway in several higher plants such as rice, *Arabidopsis*, wheat, and maize [170–172]. Studies on *Arabidopsis* seedling, rice, and alfalfa indicate that photoreactivation

greatly enhances the rate of removal of dimers, although, in the absence of photoreactivating (blue) light, dimers are slowly eliminated from bulk DNA and 6-4PPs are generally observed to be repaired more quickly than CPDs [173, 174]. Plants grown in the presence of photoreactivating radiation can eliminate the majority of both 6-4 products and CPD lesion within hours, or in some cases minutes, of their induction [30]. The structural information about the interaction between CPD lesions and photolyases became clear with the help of X-ray crystallography [175] and nuclear magnetic resonance (NMR) spectroscopy [176]. However, how DNA photolyases find lesions in the DNA molecule is still not clear [158]. It has been observed that about 240 KJ/mol of energy is captured upon absorption, out of which about 125 KJ/mol energy is consumed during the initial electron transfer from the excited FADH to CPD lesions [177]. The splitting of CPD lesion proceeds rapidly within 0.6 nanosecond [167, 178]. The back-transfer of electrons from the CPD lesion to the FADH radical is efficiently avoided by the enzyme before completion of cleavage of the cyclobutane ring [157]. With the help of ultrafast femtosecond laser spectroscopy, MacFarlane and Stanley [178] have suggested that photolyase enzyme is indeed left in the semiquinonid state after accomplishment of repair of the CPD lesion. However, Kavakli and Sancar [179] have analyzed the role of intraprotein electron transfer in photoreactivation by DNA photolyase and found that photoreduction process is not a regular part of the photolyase photocycle under physiological conditions, because the enzyme may undergo at least 25 repair cycles before losing its activity. After completion of DNA repair, a thymine pair is flipped back into the duplex DNA to form a hydrogen bond with their complementary adenine base. Fourier transform infrared spectroscopy (FTIR) has revealed that the relaxation of DNA backbone proceeds very slowly

than the repair of CPD lesions [180]. In the absence of photoreactivating light, the enzyme binds to pyr  $\diamond$  pyr and stimulates the removal of UV damage by stimulating the NER system in vivo or in vitro and defense against DNA damage even in the absence of light [181].

## 10. Excision Repair

Unlike photoreactivation, excision repair is a multistep, dark repair pathway, where an abnormal or damaged base is removed by two major subpathways: (i) base excision repair (BER) and (ii) nucleotide excision repair (NER).

**10.1. Base Excision Repair (BER).** BER is the predominant DNA repair pathway against base lesions arising from hydrolytic deamination, strong alkylating agents, ionizing radiation (IR), or by different intracellular metabolites and, indirectly, also by UV radiation via generation of ROS [182–184] and proceeds through a series of repair complexes that act at the site of DNA damage [185, 186]. The efficiency and specificity of the repair pathway are determined by several forms of DNA glycosylase which removes different types of modified bases (Table 3) by cleaving the N-glycosidic bond between the abnormal base and deoxyribose creating either an abasic site or an SSB [187]. Recently, Parsons et al. [188] have discovered that the formation of DNA repair complexes on damaged DNA stabilizes BER proteins. On the contrary, BER proteins that are not involved in repair are ubiquitinated by carboxyl terminus of Hsc70 interacting protein (CHIP) and subsequently degraded by the proteasome.

The extent of BER conservation among *E. coli* and mammals has led to progress in our understanding of mammalian BER and here, a general overview of the mammalian BER pathway will be discussed. As a result of multiple interactions with a number of repair proteins XRCC1 plays a crucial role in the coordination of BER and SSB repair [189]. The interaction between XRCC1 and polymerase  $\beta$  (Pol.  $\beta$ ) and its functional aspects was confirmed after UV-A-induced oxidative damage in living mammalian cells [190]. The AP-site is removed by the action of AP endonuclease-1 (APE-1) along with phosphodiesterase that breaks the DNA strand along 5' or 3' to the AP site, respectively, and subsequently the gap is filled by a repair DNA polymerase and the strand is joined by a DNA ligase (Figure 10) [182, 191]. It has been reported that the repair Pol.  $\beta$  itself has the capacity to excise the 5' deoxyribose phosphate residues, that is, generated by the combined actions of DNA glycosylase and ClassII AP endonuclease [192]. The major APE-1 that was discovered independently as an abasic site-specific endonuclease homologous to the *E. coli* Xth protein [193] incises duplex oligonucleotides containing 5,6-dihydroxyuracil (DHU), 5-hydroxyuracil (5-ohU), and alpha-anomeric 2'-deoxynucleosides (i.e.,  $\alpha$ dA and  $\alpha$ T) residues in human cells [194].

DNA having one nucleotide lesion is removed by short-patch BER (SP-BER) whereas two/more nucleotide lesion is repaired by long-patch BER (LP-BER) pathway [195] (Figure 10). Recently, Almeida and Sobol [184] have

proposed a unified model of SP-BER and LP-BER. On the basis of measuring the BER efficiency and presence of a single modified base in a plasmid molecule transfected into mammalian cells, Sattler et al. [196] made the first attempt to verify the occurrence of LP-BER in vivo. It is assumed that majority of repair takes place through SP-BER, initiated either by monofunctional or by bifunctional glycosylase [184]. The pathway of SP-BER after excision of damaged base involves the recruitment of poly (ADP-ribose) polymerase-1 (PARP-1) followed by scaffold protein XRCC1 and DNA pol.  $\beta$  to replace the damaged nucleotide. DNA ligase III (Lig. III) seals the nick and restores the intact DNA.

It has been observed that radiation- (X-rays,  $\gamma$ -rays) induced breaks exist mainly as 5'p and 3'p at the margin of the gap [197, 198] which is converted by the polynucleotide kinase (PNK) or APE1 into 5'P and 3'OH moieties, necessary for the DNA synthesis [199]. Unlike SP-BER, LP-BER involves proliferating cell nuclear antigen (PCNA) coupled with DNA pol.  $-\delta/\epsilon$  or  $\beta$  which extends and fills the gap by inserting 2–13 nucleotide [184]. The replication factor C (RF-C) is required to load PCNA onto the damaged DNA [195]. The flap endonuclease (Fen1) protein then displaces the ensuing DNA flap leaving a nick which is ligated by DNA ligase I (Lig. I) [200, 201].

In several plant species, some of the genes requisite for dark repair have been identified [171, 172, 202–204]. The available evidence supports the additional existence of enzyme-mediated excision-repair mechanisms in a variety of systems including pollen, whole seedlings and plants, and protoplasts derived from leaves and cultured cells [205, 206]. The formation of AP sites has been observed in seeds of *Zea mays* during early germination. This phenomenon was attributed to the action of DNA glycosylases on lesions accumulated during seed storage [207], implying the presence of BER in this species. Likewise, an enzyme activity attributed to uracil-DNA glycosylase was found in cultured cells of *Daucus carota* [208]. Recently, it has been reported that the mechanisms of BER and NER (but not photoreactivation) in higher plants are active in proliferating cells [172].

**10.2. Nucleotide Excision Repair (NER).** NER is critically important in the repair of UV-induced DNA lesions and is one of the most versatile and flexible repair systems found in most organisms but highly conserved in eukaryotes. It sorts out a wide range of structurally unrelated DNA lesions, such as CPDs and 6-4PPs caused by UVR, bulky chemical adducts, DNA-intrastrand crosslinks, and some forms of oxidative damage, that cause helical distortion of the DNA double helix as well as modification of the DNA chemistry and interfere with DNA duplication and transcription [209, 210]. Although both 6-4PPs and CPDs are removed presumably by the same NER proteins, the relative repair efficiency of both of these lesions varies considerably in mammalian cells. It has been established that in human and hamster cells, the elimination of 6-4PP is at least fivefold faster than that of CPDs [211].

Discovery of NER was first described in *E. coli* [212, 213] where about six proteins such as UvrA, B, and C

TABLE 3: DNA glycosylases and their probable substrate in bacteria, yeast, and human (modified from Sinha and Häder [22]).

Glycosylases	Organisms	Genes	Substrate
(1) Uracil DNA glycosylase	<i>E. coli</i>	<i>Ung</i>	uracil from ss- and ds-DNA
		<i>Dug/mug</i>	U from U : G, ethenocytosine, hypoxanthine and 5-hydroxycytosine
		<i>Dut</i>	?
	<i>S. cerevisiae</i>	<i>UNG</i>	Uracil
	Human	<i>UNG1/UNG2</i> <i>SMUG1</i>	uracil from ss- and ds-DNA uracil from ss-DNA, hydroxymethyluracil, formyluracil
(2) 3-methyl adenine DNA glycosylase	<i>E. coli</i>	<i>tag</i> <i>alkA</i>	3-methyladenine 3-methyladenine, 7-methylguanine, 2-methylcytosine, 5-formyluracil
	<i>S. cerevisiae</i>	<i>MAG1</i>	3-methyladenine, 7-methylguanine
	Human	<i>MPG</i> <i>Aag</i>	3-methyladenine hypoxanthine
	(3) UV-endonuclease	T4	<i>den V</i>
<i>E. coli</i>		?	?
<i>Bacillus subtilis</i>		<i>UVDE</i>	Pyrimidine dimers
<i>S. cerevisiae</i>		?	?
<i>S. pombe</i>		<i>UVDE</i>	Pyrimidine dimers
(4) Endonuclease III/thymine glycol DNA glycosylase	<i>E. coli</i>	<i>Nth</i>	5-hydroxycytosine, thymine glycol, urea oxidative DNA damage, thymine glycol and formamido-pyrimidines, oxidized pyrimidines, 2 formamido-pyrimidine-G, Me <sup>7</sup> -formamido-pyrimidine-G
	<i>S. cerevisiae</i>	<i>NTG1</i> <i>NTG2</i>	oxidative DNA damage, Thymine glycol and formamido-pyrimidines residues, 5-hydroxycytosine, oxidized pyrimidines, Me <sup>7</sup> -fapy-G
	Human	<i>NTH1</i>	oxidized guanine lesions
	(5) Endonuclease VIII	<i>E. coli</i>	<i>nei</i>
<i>S. cerevisiae</i>		?	?
Human		<i>NEIL1</i> <i>NEIL2</i> <i>NEIL3</i>	5-hydroxyuracil, 5-hydroxycytosine, 5,6-dihydrouracil, thymine glycol, formamido-pyrimidines (FapyA/G) 5-hydroxyuracil and 5-hydroxycytosine ?
(6) fapy/8-oxoguanine DNA glycosylase		<i>E. coli</i>	<i>fpg/mutM</i>
	<i>S. cerevisiae</i>	<i>OGG1</i>	2,6-diamino-5-formamidopyrimidine 8-oxoG, 2 formamidopyrimidine-G, Me <sup>7</sup> -formamidopyrimidine-G
	Human	<i>hOGG1</i>	8-hydroxyguanine, Me <sup>7</sup> -formamidopyrimidine-G
(7) A-G-mismatch DNA glycosylase	<i>E. coli</i>	<i>mut Y</i>	Adenine/C
	<i>S. pombe</i>	<i>spMYH</i>	2-aminopurine/G and A/2-aminopurine, Adenine/C
	Human	<i>MYH</i>	Adenine from G : A, 8-oxoG : A, 2-hydroxyadenine
(8) G-T-mismatch DNA glycosylase	<i>E. coli</i>	?	?
	<i>M. thermoautrophicum</i>	<i>Mig-Mth</i>	Thymine residues from T-G mismatches
	<i>S. pombe</i>	<i>thp1</i>	Uracil from G : U
	Human	<i>MBD4</i> ( $\approx$ <i>MED1</i> ) <i>TDG</i>	Thymine from T : G Recognizes a G : T mispair in a CpG sequence

TABLE 3: Continued.

Glycosylases	Organisms	Genes	Substrate
(9) Formyluracil DNA glycosylase	<i>E. coli</i>	<i>mug</i>	Formyluracil mispaired with A & G
		<i>mutM</i>	?
		<i>mutS</i>	Formyluracil mispaired with G
	<i>S. cerevisiae</i>	?	?
	Human	<i>MBD4</i> <i>hNTH1</i>	Formyluracil mispaired with G ?
(10) Hydroxymethyl uracil DNA glycosylase	<i>E. coli</i>	?	?
	<i>S. cerevisiae</i>	?	?
	Human	?	5-hydroxymethyluracil mispaired with G

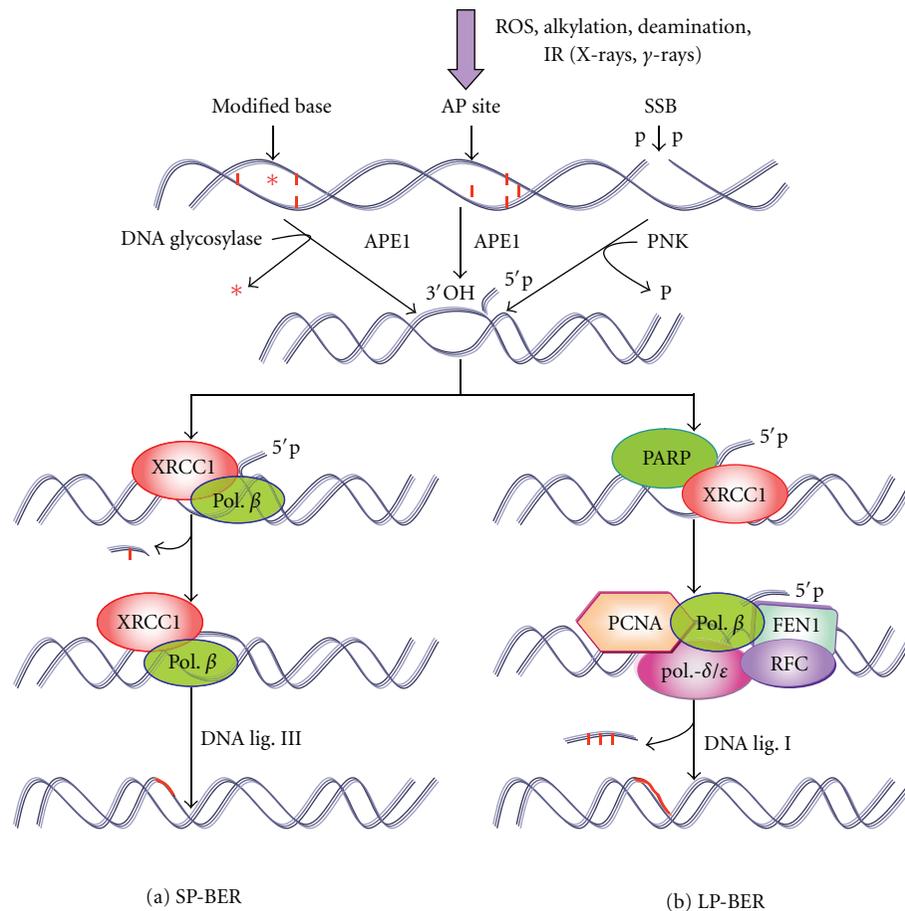


FIGURE 10: Schematic overview of mammalian SP-BER (a), and LP-BER (b). SP-BER is initiated by the activity of glycosylase and APE1, followed by scaffold protein XRCC1 and pol.  $\beta$  to remove the damaged nucleotide and DNA ligase III seals the nick. In case of LP-BER, after DNA damage by ionizing radiation, PNK is recruited to convert the damaged ends to 3'OH and 5'P moieties. Here PARP1/2, followed by XRCC1, is involved. PCNA and DNA pol.  $\beta$  and/or pol.  $-\delta/\epsilon$  extend and fill the gap by >2 nucleotides. Replication factor-C (RFC) is required to load the PCNA on DNA. Ultimately the resulting 5' flap of DNA is removed by the flap endonuclease I (FEN1) and subsequently the nick is sealed by DNA ligase I.

(known as ABC-complex, which shows excinuclease activity), UvrD (helicase II), DNA polymerase I (pol. I), and DNA ligase are recruited to complete the repair [214, 215]. Eukaryotic NER is known to be similar to prokaryotes regarding the biochemical strategy used but differs widely

in the nature and number of proteins used [210]. The eukaryotic NER pathway has extensively been studied at the molecular level in yeast and human cells. A schematic representation of the NER pathway in human is illustrated in Figure 11.

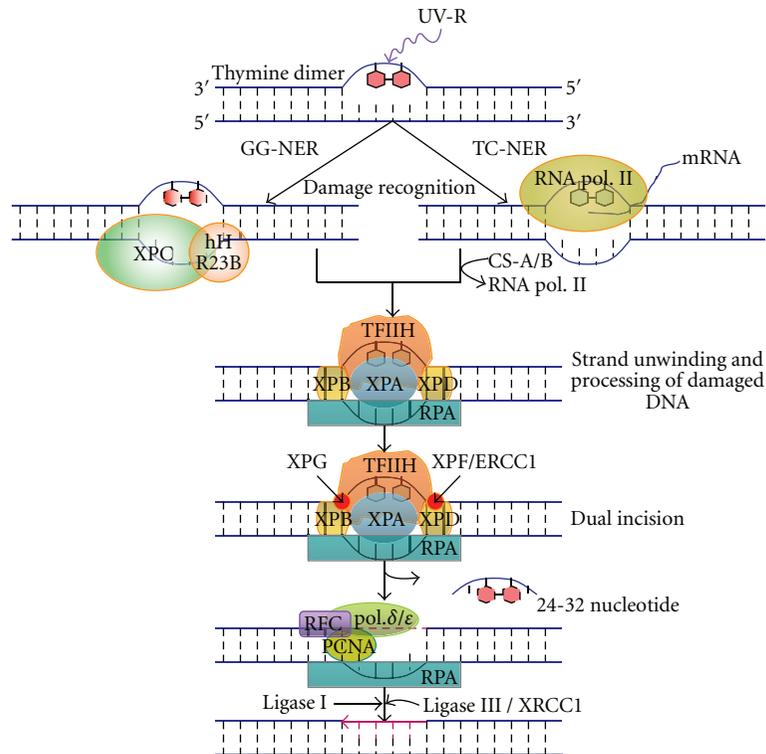


FIGURE 11: Molecular mechanisms of global genome nucleotide excision repair (GG-NER) and transcriptional coupled nucleotide excision repair (TC-NER) in mammals. For details see the text.

NER can be subdivided into differentially regulated subpathways such as global genome NER (GG-NER) and transcription-coupled NER (TC-NER): repair of lesions over the entire genome, referred to as global genome repair (GGR), and repair of transcription-blocking lesions present in transcribed DNA strands, referred to as transcription coupled repair (TCR). Both repair systems removed a wide range of UV-induced DNA lesions in a sequential way that includes damage recognition, opening of DNA double helix at damage site, and dual incisions on both sides of the lesion followed by resynthesis and ligation [210, 216] (Figure 11). In human XP-C cells, where the removal of 6-4PP takes place through the TCR pathway, the repair seems to be threefold slower as compared to normal cells. This indicates that the GGR is the most preferred and efficient pathway for 6-4PP removal [211].

## 11. Mechanistic Differences between GG- and TC-NER in Mammalian Cells

Global genome repair (GGR) is a random process that occurs gradually, whereas TCR, which is firmly linked to RNA polymerase II (RNA pol II) transcription, is highly specific and efficient. NER defects are associated with a surprisingly wide clinical heterogeneity.

It is assumed that TC-NER proceeds when the transcription machinery RNA pol II encounters a lesion. To progress the transcription-coupled repair (TCR), the stalled

polymerase must be displaced, which is brought about by the recruitment of two proteins CSA and CSB. The CSA protein (44 kDa) which belongs to “WD repeat” family of proteins exhibits structural and regulatory roles and CSB proteins (168 kDa) which belong to SWI/SNF family of proteins exhibit DNA-stimulated ATPase activity [217–219]. As stated earlier, elongation of active RNA pol II is prerequisite for efficient TCR; the CSA and CSB gene products are required for efficient repair only during the elongation stages of RNA pol II transcription. It has been suggested that the RNA pol II backs up some nucleotides upon encountering the lesion to facilitate the accessibility of the repair machinery to the lesion site [220, 221]. It is expected that the CSB protein ubiquitinates the stalled elongating RNA pol II complex at the lesion and enhances the assembly of repair factors [222]. However, the fate and the role of ubiquitylated RNA pol II have yet to be clarified [223]. Recently, Fousteri et al. [224] has revealed that CSB is a prerequisite factor in vivo to assemble NER proteins while it is not essential to recruit TFIIH or NER complex in vitro. In living human cells, Proietti-De-Santis et al. [225] have shown that CSB is required during the first phases of RNA pol II transcription initiation. At higher dose of UV radiation (i.e., used for 6-4PP detection), elongation of RNA pol II is greatly impaired, affecting the efficiency of TCR. Hence, at higher UV radiation the GGR overrules the TCR pathway [55]. The probable relationship between TCR and blockage of RNA transcription subsequent to UV-irradiation may possibly be due to CSB which acts as a chromatin remodeling

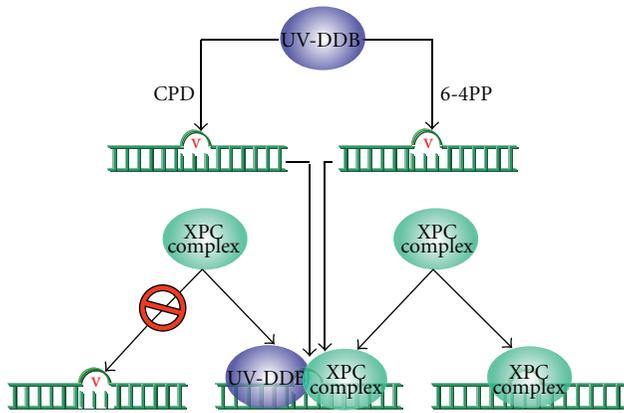


FIGURE 12: Different pathway for recognition of DNA lesions such as CPD and 6-4PP. In case of CPD photoproduct (cause little distortion), XPC complex binds to the lesion after recruitment of UV-DDB whereas 6-4PP that distorts the DNA helix to a great extent can be recognized either by interacting with prebound UV-DDB or directly by XPC complex.

factor at both levels, allowing either the recruitment of the transcription machinery at the initiation sites or the remodeling of the stalled RNA polymerase allowing the NER factors to access the lesion [223].

In GG-NER pathway, lesions produced in transcriptionally silent areas of the genome are recognized by hHR23B-XPC protein complex in an energy-independent manner. The rate of GGR strongly depends on the type of lesion. For instance, 6-4PPs are removed much faster from the genome than CPDs, possibly because of disparity in affinity of the damage sensor hHR23B-XPC. XPC is the sole XP factor not essential for TCR and is restricted to GGR [211]. It is supposed that XPC binds preferentially to the stretch of ssDNA that occurs in the nondamaged strand, opposite to a lesion [252]. However, association of UV-damaged DNA-binding protein (UV-DDB) with a cullin-based ubiquitin ligase has revealed novel mechanistic and regulatory aspects of mammalian GG-NER. It was reported that XPC and UV-DDB materialize to assist for the efficient recognition of UV-induced photolesions and that both factors are ubiquitinated [250, 253]. Lesions that cause little distortion can be recognized by the DDB complex which is also part of an E3 ubiquitin (Ub) ligase that poly-ubiquitinates XPC and XPE [216]. A mechanistic pathway for recruitment of XPC complex to the major UV-induced photolesions (i.e., CPDs and 6-4PPs) has recently been elucidated [216, 253]. It was shown that DDB complex is recruited first to the lesion (CPD) before the XPC complex, on little distorted DNA helix; however, in case of large distortion of the DNA helix caused by 6-4PPs, direct recognition by XPC is also possible for this lesion (Figure 12) [216, 253]. However, the method by which XPC locates a lesion in the vast excess of undamaged DNA in the enormous mammalian genome is not clear [254] and it needs more investigation. On the basis of DNase I footprinting, Sugawara et al. [226] showed that hHR23B-XPC attaches directly to DNA damage and alters the DNA conformation around the lesion. The

XPC protein (125 kDa) is complexed with hHR23B protein (58 kDa). These two proteins are human homologs of the yeast (*S. cerevisiae*) NER factor Rad4 and Rad23, respectively (Table 4). In mammalian cells, the quantity of hHR23B is higher than the XPC [255] and *in vitro* activation of the later protein is stimulated by hHR23B possibly in a structural quite than a catalytic way [256, 257]. It has been assumed that hHR23A can substitute for hHR23B in complex formation and stimulation of XPC repair activity [258]. Both hHR23A and -B harbor a ubiquitin-like moiety at their amino terminus [230]. hHR23B-XPC complex or only XPC exhibits a similar high affinity for both UV-induced single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) [230, 259], preferentially binds to DNA with various lesions [259] and even to small bubble structures with or without a lesion [260]. hHR23B-XPC is absolutely required for dual incision as well as for open complex formation during GG-NER [243, 261]. Overall, it has been distinguished that RNA pol II with the recruitment of two proteins (i.e., CSA and CSB) proceeds the TCR while hHR23B-XPC complex is the first factor in NER that initiates GGR by sensing and binding lesions, locally distorting the DNA double helix and recruiting the other factors of the system [227].

After initial steps of damage recognition, the subsequent pathway for both GGR and TCR system is almost similar. The unwinding of DNA double helix at the site of lesion takes place by the components of multi-subunit transcription factor-IIH (TFIIH). TFIIH is a ten-subunit protein complex (Table 4) composed of a core complex (XPB, XPD, p62, p44, p34, p52, p8) and of a cdk activating kinase (CAK) subunit (Mat1, Cdk7, CyclinH) [236]. TFIIH is usually involved in initiation of RNA Pol II transcription, but upon DNA damage can be employed in cell cycle regulation and NER (both in global genome and TC-NER) [228, 235]. Two subunits of TFIIH such as XPB (3' to 5' helicase) and XPD (5' to 3' helicase) are responsible for opening of DNA double helix around the lesion in an energy (ATP) dependent manner. It has been found that the XPD helicase activity is dispensable for *in vitro* transcription [262] but seems to play an additional architectural role within the complex by connecting the core TFIIH with the CAK subunit [228, 236]. After opening of DNA double helix by TFIIH, three proteins such as RPA, XPA, and XPG are recruited. The exact order of assembly of these proteins is not clear. Both XPA and RPA can recruit with the DNA lesions in absence of XPG, and similarly XPG can also join the damage sites in the absence of XPA [238, 239]. Moreover, XPA and heterotrimeric replication protein A (RPA; RPA70, 32 and 14) are recruited to confirm the presence of DNA damage and form a more stable preincision complex [185]. RPA was found to be required both for the dual incision and for the repair synthesis steps of NER [263]. It was assumed that RPA binds the nondamaged strand of the opened DNA bubble, thus allowing exact positioning and stimulation of the endonuclease activities of XPG and ERCC1-XPF [246, 247]. XPG, which belongs to flap endonuclease-1 (FEN-1) family of structure-specific endonucleases [264], is not only involved in performing the 3' incision in NER but also required for stabilizing the fully open DNA bubble structure

TABLE 4: NER proteins and their probable role in human and *S. cerevisiae*.

NER Factors	Name			Function	References
	Human	Yeast <i>S. cerevisiae</i>	Size (a.a)		
XPC-hHR23B	XPC	Rad4	940	Binds damaged DNA; recruits other NER proteins; works with hHR23B. involved only in GGR	[22, 226, 227]
	hHR23B	Rad23	409	Stimulates XPC activity <i>in vitro</i> ; contains ubiquitin domain	[22, 227–229]
	hHR23A	Rad23	363	Can substitute for hHR23B <i>in vitro</i>	[227, 230]
	CEN2	—	172	Stabilizes the XPC-hHR23B complex	[216, 231]
TFIIH	XPB	Rad25/SSL2	782	3' → 5' helicase	[227, 232, 233]
	XPD	Rad3	760	5' → 3' helicase	[227, 233, 234]
	p34	TFB4	303	DNA binding?	[227, 228, 235]
	p44	SSL1	395	DNA binding?	[227, 228, 233]
	p62	TFB1	548	Core TFIIH subunit	[227, 228, 236]
	p52	TFB2	462	Core TFIIH subunit	[227, 228, 233, 236]
	Mat1	TFB3	309	CDK assembly factor; CAK subcomplex	[227, 228]
	Cdk7	Kin28	346	CDK, C-terminal domain kinase; (CAK) subcomplex; phosphorylates RNA pol. II and other substrates	[227, 228]
	Cyclin H	CCL1	323	Cyclin; CAK subcomplex	[227, 228]
	TFB5/TTDA (p8)	Tfb5	71	Stabilizing subunit	[228, 237]
XPA	XPA	Rad14	273	Binds damaged DNA and facilitates repair complex assembly; affinity for ssDNA	[183, 238, 239]
RPA	RPA70	Rfa1	616	Stabilizes opened DNA complex; positions nucleases; ssDNA binding	[227, 240–242]
	RPA32	Rfa2	270	Stabilizes opened DNA complex; positions nucleases; ssDNA binding	[227, 240–242]
	RPA14	Rfa3	121	Stabilizes open complex (with XPA/Rad14)	[22, 240, 241]
XPG	XPG	Rad2	1186	Endonuclease (catalyzes 3' incision); stabilizes full open complex	[228, 243–245]
ERCC1-XPF	ERCC1	Rad10	297	Part of structure-specific endonuclease; catalyzes 5' incision; interstrand cross-link repair	[227, 246–248]
	XPF	Rad1	905	Part of endonuclease (5'-incision); recombination via single-strand annealing	[227, 246, 249]
DDB	DDB1	—	1140	CPD recognition?	[228, 250, 251]
	DDB2	—	428	Chromatin remodeling?	[228, 251]

and to permit the 5' incision by ERCC1-XPF [265]. Subsequently, the injured part of the DNA is removed by cleaving the damaged strand towards 3' and 5' of the lesion by endonuclease XPG and XPF/ERCC1 complex, respectively, generating a 24–32 base oligonucleotide fragment [183]. It has been found that E2F1 plays a direct, non-transcriptional role in DNA repair involving increased recruitment of NER factors to sites of UV-induced DNA damage [266]. Finally the gap is filled by DNA polymerase  $\delta$  or  $\epsilon$  (along with some accessory proteins, like PCNA and RFC) and sealed

by DNA ligase. It is assumed that ligase-I is responsible for ligation of remaining nick [267], but very recently it has been reported that mostly ligase III, in cooperation with its partner XRCC1 seals the DNA nicks and ligase I plays a minor role in actively replicating cells, but not in quiescent cells [268]. Recently, several workers have tried to dissect the molecular mechanisms of TC-NER [216, 223, 244, 269]. In spite of the above facts, more investigations are still required to improve our understanding of the GGR and TCR pathways.

Several observations provide evidence that “dark” repair of UV-induced NER is a significant DNA repair mechanisms in plants that is capable of excising dimers, particularly 6-4PPs [30, 270]. Genetic and genomic analysis indicates that plant NER pathway is homologous to that of mammals and fungi and unrelated to the bacterial system [204, 271–273]. Based on the reduction of nuclear CPD frequency, the presence of NER has been reported to occur in several plants such as *Glycine max* and cultivars of *Oryza sativa* [274, 275]. Furthermore, CPDs were found to be excised from the nuclear DNA of *Daucus carota* and *Wolffia microscopia* at rates dependent on damage levels and comparable to those in animal cells [205, 275]. A UV-specific endonuclease resembling UvrABC nuclease in activity was partially characterized from spinach [206]. Classical genetic analysis has resulted in the identification of at least four complementation groups required for this repair in *Arabidopsis* (*UVR1*, *UVR5*, *UVR7* and *UVR1*) [276–278] and many more UV-sensitive mutants await further genetic and phenotypic characterization [206]. Moreover, a plant homologue of human NER gene of the endonuclease, *ERCC1*, has been cloned from *Lilium longiflorum* which showed a similar role in DNA repair in plants [279].

## 12. Recombinational Repair

It is one of the widespread mechanisms which efficiently repair double-strand breaks (DSBs) and single-strand gaps in damaged DNA by a series of complex biochemical reactions, as a result of ionizing radiation, UVR, ROS, and chemotherapeutic genotoxic chemicals [5]. The lethal effects of double strand breaks (DSBs) can be conquered by the existence of two independent pathway, such as homologous recombination (HR) and non-homologous end joining (NHEJ). Multiple proteins are required for DSB repair by recombination, which are conserved among all eukaryotes and deficiencies in this repair mechanism can cause hereditary diseases. For instance, mutation of at least one of these repair proteins, called BRCA1 may lead to hereditary breast cancer [280]. Evidence suggests that BRCA1 could be one of the key players in DNA damage response [281]. DSB repair through HR process is an error free pathway, since, it requires an extensive region of sequence homology between the damaged and template strands, whereas NHEJ is an error prone, alternate pathway for the repair of DSBs, essentially joins broken chromosomal ends independent of sequence homology.

**12.1. Homologous Recombination.** Repair of DSBs by HR requires the genes of “RAD52 epistasis group” such as *RAD50*, *RAD51*, *RAD52*, *RAD54*, *RAD55*, *RAD57*, *RAD59*, *MRE11* and *XRS2*, which were first defined in yeast *Saccharomyces cerevisiae* mutants. Homologues of most of the genes are highly conserved among all eukaryotes including human [282, 283] highlighting these genes for cell survival. Among all, *E. coli recA* gene and its eukaryotic homologs *RAD51s* are the best recombination genes [284]. The *recA* gene encodes a DNA-dependent ATPase that binds to

ssDNA and promotes strand invasion and exchange between homologous DNA molecules [285]. Among eukaryotes, the yeast *S. cerevisiae* and *Schizosaccharomyces pombe* have four *RAD51*-like genes (*RAD51*, *DMC1*, *RAD55/rhp55*, and *RAD57/rhp57*) [286, 287] whereas vertebrate animals and plants have seven types of *RAD51*-like genes (*RAD51*, *-51B*, *-51C*, *-51D*, *DMC1*, *XRCC2*, and *XRCC3*) [288]. The eukaryotic *RAD51s* play a significant role in HR, maintaining genome integrity in both mitotic as well as meiotic cell cycle [288, 289]. There are 59% identity between *S. cerevisiae*, human and mouse in the case of Rad51 protein (Rad51p) and 30% identity to RecA protein of bacteria [290], whereas yeast and human proteins are 60% identical in case of Rad52 proteins (Rad52p) [291]. Yeast cell can exhibit both “allelic” [292, 293] as well as “ecotopic recombination” [294, 295] to repair a broken chromosome. Recombinational repair is a significant UV-tolerance mechanism in plants where UV-induced chromosomal rearrangements including homologous intrachromosomal recombination events have been found [296]. In mammalian cells the recombinational pathway of DSBs, seems to be operated in late S- and G2-phase, when DNA molecules are replicated and spatially juxtaposed [297].

The first step of DSB repair *via* HR is the resection of 5′ ends to produce a 3′ ssDNA overhang by means of an exonuclease (such as RecBCD in *E. coli*, MRX-complex in *S. cerevisiae* and MRN-complex in vertebrates). Rad51 (a functional homolog of the *E. coli* RecA) [298] is the central protein in HR, binds the exposed single-stranded tails forming a nucleoprotein filament and this early step is promoted by a Rad55/Rad57 protein heterodimer [299] by overcoming the inhibitory effects of the heterotrimeric single-stranded DNA binding protein RPA [300]. Recently, it has been reported that a member of the histone H2A family,  $\gamma$ -H2AX protein plays an important role in the recruitment of Rad51 protein in HR in eukaryotes [301]. The Rad51 nucleoprotein filament in association with other repair protein searches the genome for an intact copy of the broken DNA on the sister chromatid to form a heteroduplex joint molecules or D-loop that is matured in to a Holliday junctions (HJs). HJ is then resolved to give crossover products (Figure 13). In *E. coli*, this HJ is resolved by the positioning of RuvABC resolvosome, however in eukaryotic cell, how this HJ is resolved to give crossover products is not known. In *S. cerevisiae*, DNA DSB repair by forming noncrossover product has been reported which does not involve the processing of a double HJ structure. Virtually, the joint molecule formation is followed by extension of the incoming strand by DNA polymerases and branch migration, leading to restoration of the genetic information [283, 302].

**12.2. Non-Homologous End Joining.** When HR is inactivated, an alternate pathway, that is, NHEJ becomes operative for the repair of DSBs [303], that also involves a multi-protein complex and has been found in organisms ranging from a few prokaryotes to mammals. This suggests that this mechanism has been conserved during the course of

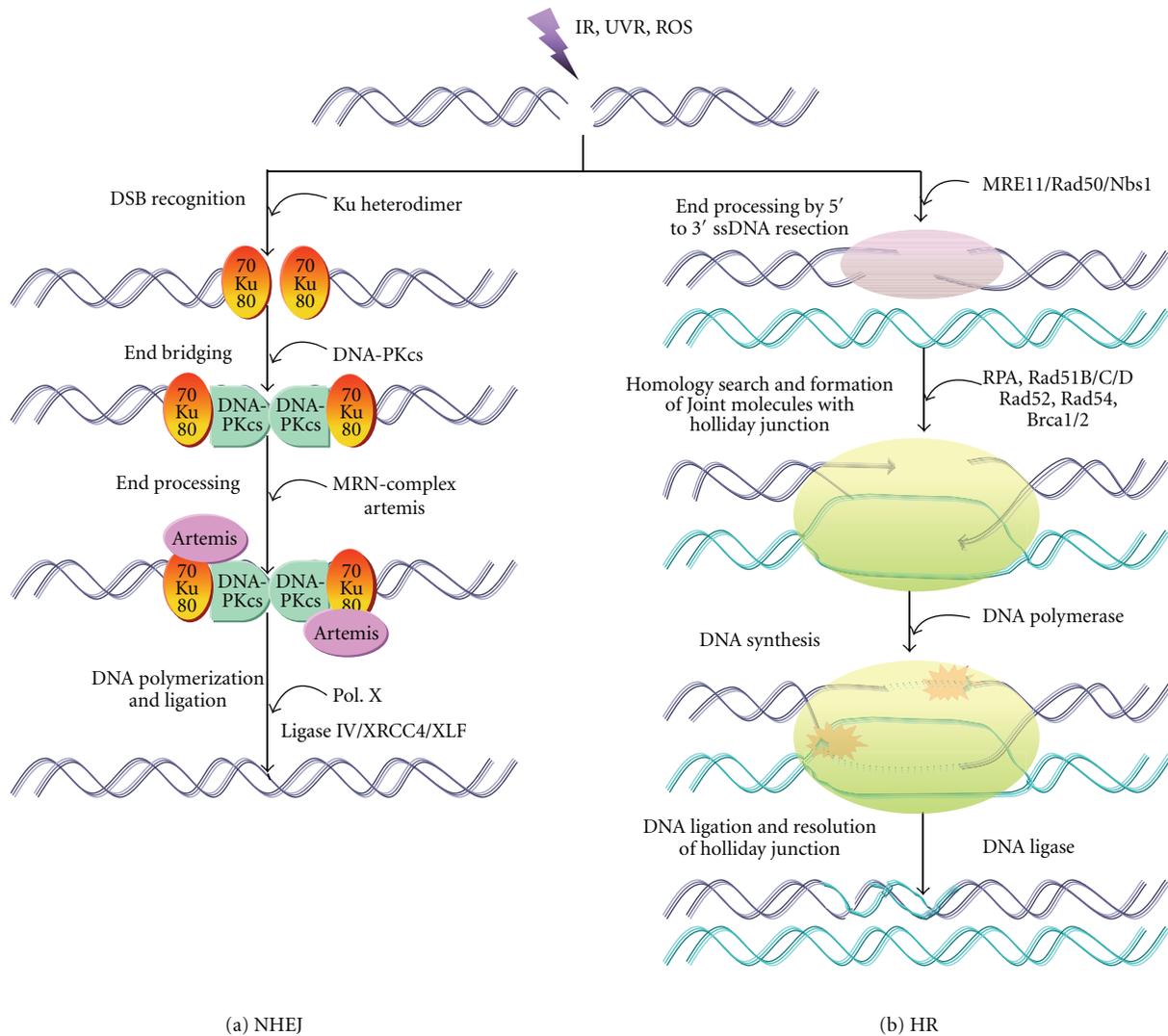


FIGURE 13: Schematic representation of recombinational repair by (a) non-homologous end joining (NHEJ), and (b) homologous recombination (HR).

evolution, although, most of the protein factors, involved in NHEJ were initially identified in the mammalian cells [304]. Most of the DSBs produced by DNA damaging agents, do not have ligatable termini, hence requires the action of nucleases and DNA polymerases to generate them. The participation of DNA polymerase in the NHEJ pathways is still a matter of debate, however in vitro biochemical analysis in mammals, suggest that DNA polymerase  $\lambda$  (Pol.  $\lambda$ ) and/or polymerase  $\mu$  (Pol.  $\mu$ ) participates in NHEJ process at incompatible DNA ends [80, 305, 306]. The NHEJ process is initiated by the binding of specific protein to the broken ends, which may acts as end bridging factor [307]. It has been shown that Ku complex (a heterodimer of Ku70/Ku80 [ $\approx 86$ ]) is a major end binding factor in mammalian cells, possess end bridging activity [308, 309]. The catalytic subunit of DNA protein kinase (DNA-PKcs) is required in mammalian NHEJ to bridge the DNA ends through their protein-protein interactions [310, 311]. Cells lacking functional DNA-PK

components are known to have elevated sensitivity toward UV irradiation [312].

Association of DNA-PKcs is followed by the recruitment of other repair proteins (such as ligaseIV/Xrcc4, Artemis, PNK and Polymerase X) to proceed the NHEJ repair [304] (Figure 13). Recently, a third protein, designated as XLF or Cernunnos [313] that has homology to Xrcc4, has been identified and shown to co-associate with the DNA ligaseIV/Xrcc4 complex [314, 315]. Artemis, a member of  $\beta$ -lactamase superfamily, has 5'  $\rightarrow$  3' exonuclease activity. In the presence of DNA-PKcs, Artemis can also function as a 5'  $\rightarrow$  3' endonuclease. It has been found that Artemis dependant DSB rejoining also requires ATM, Mre11-Rad50-Nbs1 (MRN) complex, 53BP1 and H2AX [316–318]. The yeast Hdf1/2 and Dnl4/Lif1 are the functional homology of mammalian Ku and DNA ligaseIV/Xrcc4, respectively. DNA ligase IV is absent in bacteria, however, in *Bacillus subtilis*, the gene *ykou/v* has been found that encodes a

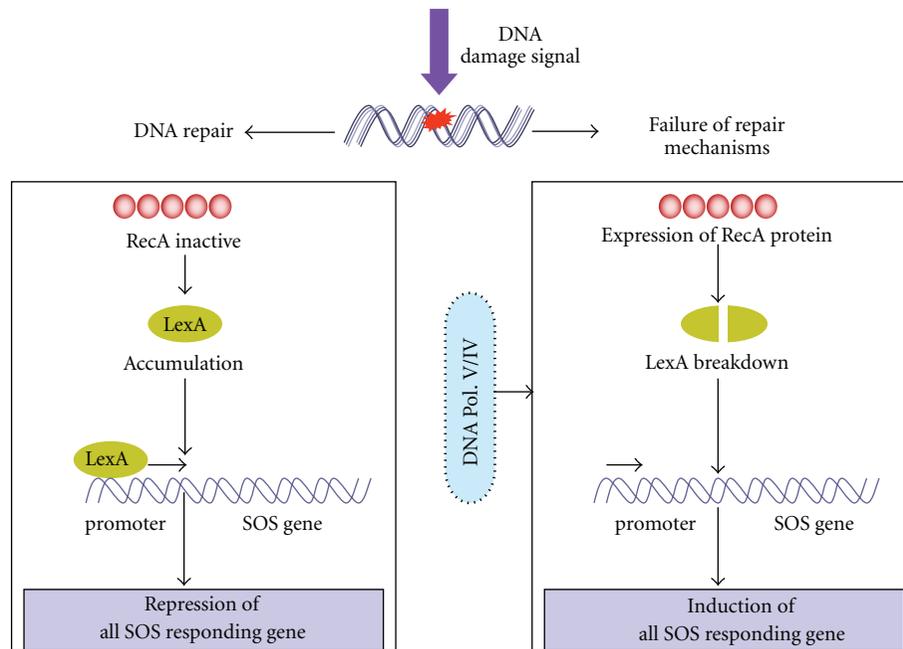


FIGURE 14: SOS response: As a result of massive DNA damage and failure of all possible repair mechanisms, RecA proteins is expressed, which activate the auto breakdown of LexA proteins, allowing the induction of all SOS responding genes. The pathway of SOS response is reversed when damages are repaired through the damage specific mechanisms. Here the inactivation of RecA protein allows the accumulation of LexA, which bind to SOS promoters and repress all SOS responding genes. SOS response is highly mutagenic due to involvement of DNA polymerase V/IV.

polypeptide with ligase, primase and nuclease domains. Genetic and biochemical evidence suggest that Mre11-Rad50-Xrs2 (MRX) act as end bridging factor in yeast NHEJ, since DNA-PKcs is absent in them [319, 320]. In case of bacteria, the Ku proteins occur in homodimeric forms and exhibits homology with eukaryotic Ku protein in some extent [321]. Recombinational repair is a significant UV tolerance mechanism in plants where UV-induced chromosomal rearrangements including homologous intrachromosomal recombination events have been found [296]. Very few of the plant genes involved in DSB repair have been identified. The sequence of an *Arabidopsis* Rad51 homologue has been made available [322]. It has been suggested that as in mammals, breaks are repaired by nonhomologous recombination far more frequently than *via* HR [202, 323].

### 13. SOS Repair/Response

The accumulation of massive amount of DNA lesions within the cells under different specific physiological responses [324] may lead to the occurrence of SOS repair system which was well described in *E. coli*, where the involvement of more than 40 genes have been found [325]. It has been found that the bacterial NER is linked with all DNA damage response through a network of reactions, known as SOS response [326].

The accumulation of DNA lesions may interfere with replication process, prompting cells to stop division, therefore giving time to the cell to repair damaged DNA and

proceeds DNA replication process [324]. SOS repair system is initiated by interaction of two crucial proteins the RecA and the LexA repressor which curbs the expression of SOS genes by binding to their promoters [327] (Figure 14). The proteolytic activity of RecA protein inactivates the LexA repressor and induces all the genes to which LexA is associated. A number of genes (or operon) collectively known as din (damage inducible) gene such as *uvrA*, *uvrB*, *cho* (*uvrC* homolog) and *uvrD* of *E. coli* NER take part in SOS response [325, 328]. The SOS response is induced with damage signal but it is highly mutagenic due to engagement of error-prone DNA polymerase V (UmuC/UmuD<sub>2</sub> complex) [329] and DNA polymerase IV [330] in *E. coli*. Interestingly, it has been found that DNA polymerase IV (*dinB*) is also involved in translesion synthesis in *E. coli* [331]. Majchrzak et al. [324] examined the effects of SOS response on genome stability of trinucleotide repeat sequences (TRS) in *E. coli* and observed that SOS response genes destabilized the TRS tracts and also altered the superhelical density of the plasmids. Recently, the genes *imuA* and *imuB* have been described that induce SOS mutagenesis in *Caulobacter crescentus*, but absent in *E. coli* [332]. However, the number of genes responsible for SOS repair system has still to be investigated.

### 14. Cell-Cycle Checkpoint Activation

In response to diverse genotoxic stresses such as UV radiation, IR, chemicals used in medical therapy, by-products of intra-cellular metabolism, several protective mechanisms

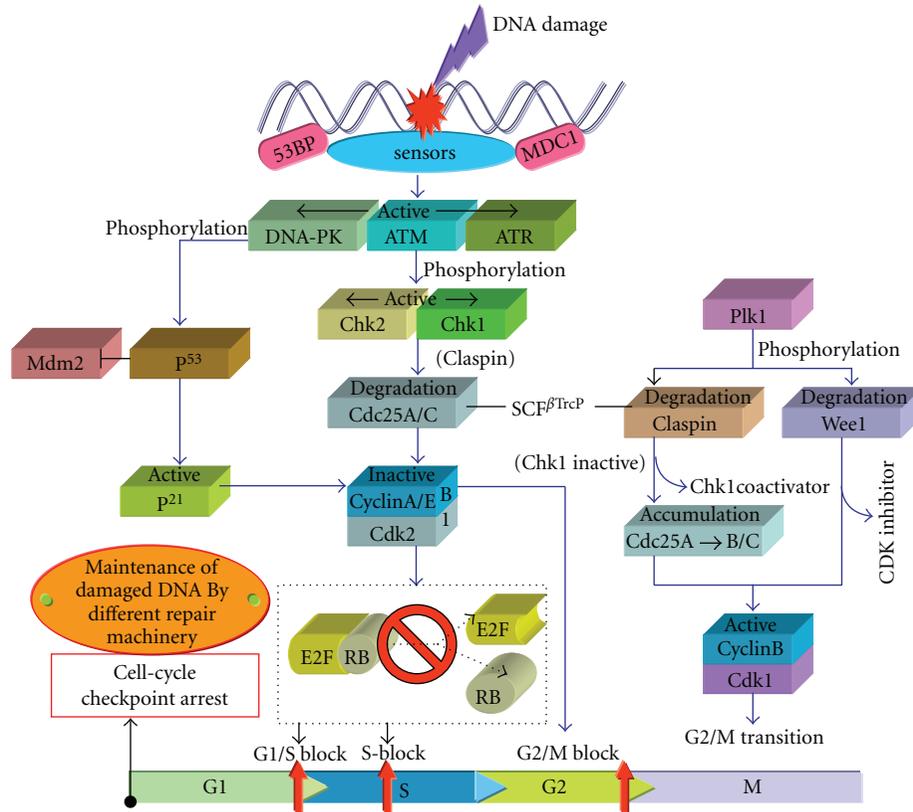


FIGURE 15: Schematic illustration of DNA damage-induced cell-cycle checkpoint activation (for details, see text).

including processes of DNA repair, Cell-cycle checkpoint arrest and apoptosis (programmed cell death) develop within the organisms to secure the genomic integrity. DNA damage such as altered DNA bases, abasic site, DNA lesions (CPDs/6-4PPs), strand breaks (DSBs/SSBs) may stop the progression of cell-cycle temporarily to give opportunities to the cell for DNA repair before replication or segregation of the affected chromosome [333], or may induce an apoptotic program to eliminate the damaged cells to avoid their carcinogenic potential [334]. ROS may induce several types of DNA lesions such as DSBs and SSBs, DNA-DNA and DNA-protein cross links and base modifications [335]. It has been shown that most of the chromosomal translocations produce via aberrant processing of a DNA DSBs. Hence forth, we discuss the DSBs/SSBs-induced cell-cycle checkpoint arrest in eukaryotes mainly in mammals that play a critical role in preventing chromosomal instability. Regulation of cell-cycle checkpoint proceeds through a network of damage sensors, signal transducers, mediators, and various effector proteins [183]. Phosphatidylinositol-3 (PI3)-kinase related kinases (PIKKs) ATM (ataxia telangiectasia mutated) protein, ATR (ATM and Rad3 related) protein, and DNA-PK, with effector proteins mediated cell-cycle checkpoint arrest (at G1/S, G2/M, and intra S-phase), DNA repair and cell death have been observed in mammalian cells [336]. It has been shown that ATM and DNA-PK are activated by the presence of DSBs where as activation of ATR takes place by single strand regions of DNA [337, 338]. Activation of both ATM

and ATR results in phosphorylation of Chk2 and Chk1 respectively which transfer the DNA damage signal to the cell-division cycle proteins Cdc25(A-C). Phosphorylation of Cdc25 by Chk1/Chk2 leads to its ubiquitin mediated degradation that results in G1 and S-phase arrest (Figure 15). The prevailing evidence suggests that damage response mediated activation of ATM/ATR either directly or *via* Chk2 phosphorylates p53, which transcriptionally activates the Cdk inhibitor, p21, which arrest G1/S cell-cycle checkpoint [336]. Recently, it has been reported that DNA damage caused by UV radiation or ROS such as hydroxyl (OH) free-radical results in ATM mediated phosphorylation of BID protein that induce cell-cycle arrest in S-phase [339, 340]. The occurrence of DNA damage response in G2-phase, leads to checkpoint mediator (claspin) dependent activation of Chk1/2, followed by SCF<sup>βTrcP</sup> mediated degradation of CDK-activating phosphatase Cdc25A [341, 342], that results in arrest of multiple cell-cycle transition including the G2 checkpoint [343, 344]. The ubiquitin mediated destruction of claspin and WEE1 (both proteins have conserved β-TrcP phosphodegrons) eliminates the essential coactivator of Chk1 and CDK inhibitor respectively allowing reaccumulation of Cdc25A followed by Cdc25B and C, which results in activation of cyclin-Cdk (cyclinB-Cdk1) complex [345]. Under normal conditions, this latter complex being active promotes G2/M transition and upon inactivation due to DNA damage, blocks the G2 cell-cycle and unlike the G1/S checkpoint this arrest seems to be partly p53/p21

independent [183]. The intermediate component of this pathway is  $\beta$ -TrcP (an adaptor protein) that links both WEE1 [346] and claspin [347–349] with the SCF ubiquitin ligase complex and this SCF <sup>$\beta$ TrcP</sup> acts as trigger of checkpoint initiation where recognition of phosphodegron  $\beta$ -TrcP is exposed after Chk1 mediated Phosphorylation of Cdc25A [350], as well as checkpoint recovery which is linked with Plk1 mediated phosphorylation of claspin and WEE1 [347, 348]. Although, the exact mechanism(s) regarding the reactivation of Plk1 during checkpoint recovery is still in dispute. The malfunctioning of cell-cycle checkpoint as a result of chronic damage and/or defects in DNA damage response (DDR) components such as p53, p21, ATM, Chk2, BRCA1/2 tumor suppressors, may induce several types of human disorder at the expense of enhanced genomic instability [351].

In addition to the above mentioned repair mechanisms several other repair machineries such as mutagenic repair (or lesion bypass) and programmed cell death (PCD) or apoptosis may become effective for the recovery of genome against constant attack of numerous genotoxins. UV-radiation, ionizing radiation and various chemicals are responsible for most of the mutagenesis due to a process of translesion synthesis in which a polymerase or replicative assembly encounters a noncoding or miscoding lesion, inserts an incorrect nucleotide opposite the lesion and then continues elongation [5]. It has been reported that translesion synthesis past a CPD, facilitated by pol.  $\eta$ , with the insertion of adenines opposite both bases of a T<sup>^</sup>T CPD [352], where as 6-4TT may lead to a G insertion. In *Saccharomyces cerevisiae*, pol.  $\eta$  and pol.  $\zeta$  (consisting of Rev3 and Rev7 proteins) has been reported to replicate across a T<sup>^</sup>T CPD [353]. Polymerase  $\eta$  (pol.  $\eta$ ) can also replicate across a basic sites, AAF (acetylaminofluorene), guanine adducts and cis-platinated guanines [352].

When the repair mechanisms are unsuccessful, it may cause cellular senescence (permanent cell cycle arrest), oncogenesis or apoptosis [354]. Apoptosis plays an essential role in survival of the organisms by preventing the multiplication of mutated chromosomes, normal embryonic development, elimination of indisposed cells and maintenance of cell homeostasis.

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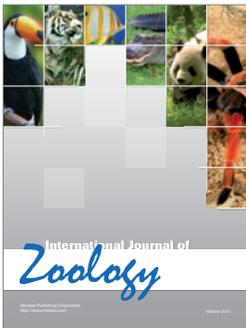
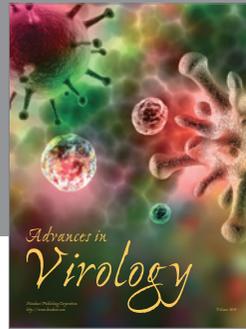
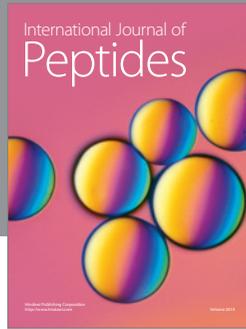
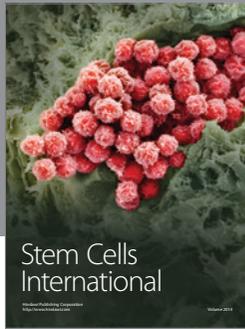
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