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DNA Repair, Cancer and Cancer Therapy - The Current State of Art

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1. Introduction

Since the demonstration of double stranded DNA structure by Watson and Crick in 1953, knowledge about DNA structure and sequences has accumulated (Alberts et al., 2008). Although DNA contains complex genetic information in a very stable manner, DNA sequence and/or structure are sometimes disrupted. Previous research on the damage and repair mechanisms of DNA complex showed the existence of various types of DNA damage as well as the presence of sophisticated processes utilized by the cells to maintain the integrity of genome. DNA damage can be defined as any changes in the genomic integrity due to the disruptive impact of any exogenous and endogenous factors. Interestingly, it has been shown that damage to DNA is a usual event which is also underlying cause of many disorders including certain mutations and deletions leading to cancer and other inherited or acquired pathologies.

There are many endogenous and exogenous sources which cause DNA damages interfering with genome. Endogenous factors emerge from the DNA replication as well as recombination (Martin, 2008a). Although some of the exogenous factors may directly react with DNA, some of them tend to cause DNA damage by indirect route. Oxidation damage, alkylation of bases, hydrolysis of bases and replication errors are considered to be endogenous factors. Ultraviolet light, ionizing radiation and environmental chemical agents are among the exogenous factors.

1.1 Damage exerted by endogenous factors

1.1.1 Oxidative damage to bases

Normal metabolic events and external factors can lead to the formation of reactive oxygen species (ROS). ROS are molecules that contain an unpaired electron in their utmost outer orbital, which makes them very reactive. Generally, the ROS are superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$) and hydroxyl radicals ($^{\cdot}OH$). These agents can oxidize DNA, causing damage such as oxidized bases, single strand and double strand breaks.

Oxidatively damaged nucleotides can be found common in cells despite the extensive DNA repair. Not surprisingly, the amount of this damage is higher in cancer cells (Iida et al.,

2001). There are various ways by which the cell can endure the damage or decrease the number of the ROS (Slupphaug et al., 2003). Oxidative stress is observed when the natural antioxidant capacity of the cell cannot tolerate the ROS production. This results in the damage of the macromolecules such as DNA, proteins and lipids. ROS also affects the antioxidant enzymes as well (Tabatabaie et al., 1994). Studies have emphasized that any increase in the endogenous ROS generation or decrease in cellular antioxidants increases the mutation rate and inevitably raise the risk of cancer. Consuming antioxidant- rich diet has been proven to decrease the risk of cancer (Loft & Poulsen, 1996).

1.1.2 Alkylation of bases: Methylation

Oxygen is not the only reason of DNA damage in cells. Alkylating agents such as S-adenosylmethionine (SAM), which is a reactive methyl group donor, play significant roles in DNA damage. SAM methylates DNA, which is important for regulation of gene expression (Holliday & Ho, 1998) (Fig. 1). Endogenous methylation can also be carried out by betaine, choline and simple alkylating agents. Although this may occur endogenously, they might also be obtained from exogenous sources by environmental pollution and/or tobacco.

Most frequently, DNA methylation generates 7-methylguanine and 3-methyladenine. Having no effect on the coding specificity of the base, 7-methylguanine can be considered as less harmful (Zhao et al., 1999). However it can cause the blocking of DNA replication by the destabilization of the glycosyl bond. 3-methyladenine also blocks replication. DNA glycosylase is present in all living cells, removing 3-methyladenine from DNA. However, this action is found to be decreasing by age. 7-methylguanine repair is very insufficient and its accumulation can be observed in mammalian DNA (Atamna et al., 2000).

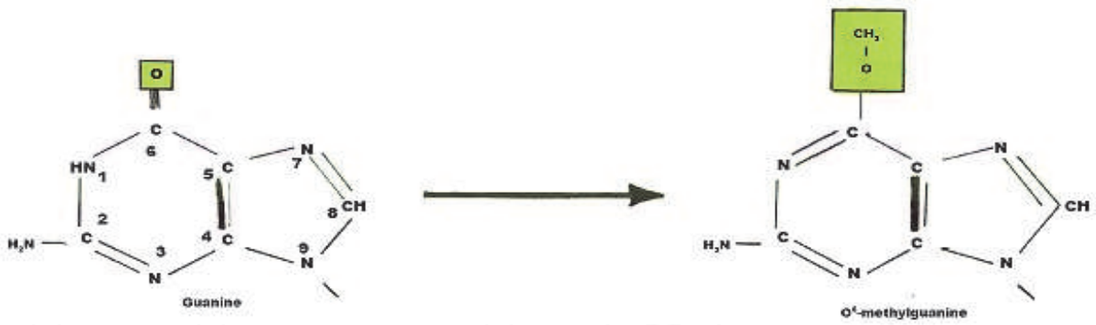

Fig. 1. Alkylation of bases

1.1.3 Hydrolysis of bases: Deamination, depurination / depirimidation

Hydrolytic damage causes depurination, depyrimidination, and deamination of bases. The glycosidic bond in DNA structure is prone to breakage under heating, alkylation of bases or N-glycosylase activity (Lindahl et al., 1982). An abasic site is the result of the glycosidic bond cleavage in DNA. Apurinic (AP) sites can be produced spontaneously or by the effect of ROS (Nakamura et al, 2000). Abasic sites are among the most common endogenous lesions estimated to be 10 000 lesions/ cell/day. Hydrolytic deamination takes place frequently in DNA bases; however it is more frequent in single stranded DNA than double stranded. Deamination and methylation processes affect amino containing bases, cytosine, and adenine. In a cell, daily between 100 to 500 cytosines are deaminated to uracil. Deamination and methylation converts cytosine into uracil and/or mutant thymidine leading to wrong base pairs (Lindahl, 1993).

Human cells lose about 5000 adenines or guanines everyday because of spontaneous base-sugar link fissions. Less frequently, adenines spontaneously deaminate to give hypoxanthine (Alberts et al., 2008).

1.1.4 Errors in replication

In humans, 10^7 cells divide every second and it is estimated that one-third of these spontaneous mutations take place. These mutations are caused by mistakes in DNA replication and the copying of damaged templates by DNA polymerases. Scientists things that, errors mostly coused by mispairing of bases with different nature. This means pairing of nontautomeric chemical forms of different bases or pairing of normal bases but mismacth which is caused by a little shift of nucleotide positions. This mispairing is named as wobble and it occurs because the flexiblelty of DNA double helix (Crick, 1966).

Any undetected error in replication will lead to mutant cell due to mismacth, (for example, mutant strand containing CG instead of AT). Fortunately, rate of replication error is as low as $1/10^5$ and with proof-reading mechanism this rate reduces up to $1/10^7$-$1/10^9$ (Johnson et al., 2000).

1.2 Damage exerted by exogenous factors: Exogenous factors are composed of two main sources

1.2.1 Physical factors: UV light and ionizing radiation

Ultraviolet (UV) radiation, as a physical factor, is of solar origin and one of the most powerful exogenous agents disrupting genomic sequence. UV light is composed of three subtypes, UV-A, UV-B, UV-C. All has different wavelengths resulting in various effects on DNA. Compared with UV-A, UV-B has shorter wavelength (280-315 nm) and a more direct effect on DNA. It modifies chemical composition of DNA by forming dimers which disrupts molecular composition (Rastogi, 2010). TT dimerization is the most encountered form of UV-related damage. Thymidine dimers interfere with DNA replication by changing DNA polymerase (Arlett et al., 2006). Fortunately, UV-B radiation occupies a very small part of total solar energy. UV-A has weaker impact on DNA sequence because of its poor absorption by DNA. But, it tends to produce $^1O_2$ which can disrupt DNA sequence. This way is the indirect damaging of UV-A light on DNA. UV-C does not lead to considerable hazard on cells owing to its high absorption in atmosphere.

Radiation is also known to interfere with genome integrity. The mechanisms of the damage to DNA are as follows ;

- Rupture of the strand: It can divide as single or double strand breaks. Single strand breaks (SSBs) may occur at the phosphodiester bond, or at the bond between the sugar and the base. A large proportion of the SSBs are caused by $OH^{\cdot}$. Double strand breaks (DSBs) involve breakage of both strands and are directly proportional to the radiation dosage.
- Alteration of bases: Bases can be damaged or destroyed by radiation. Among the bases, pyrimidines (T, C) are more vulnerable to radiation than purines.
- Destruction of sugars.
- Cross-links and formation of dimers (Alberts et al., 2008).

1.2.2 Chemical agents

Over a century, exposure to chemical agents has been known to induce cancer. After many studies on individuals who work with chemicals or exposed to the chemicals, researchers demonstrated the basic principles of chemical carcinogenesis. This chemicals establish

covalent bounds with bases on DNA and create DNA adducts. This structure is accepted as beginning of carcinogenesis (Poirier, 2004). Chemicals can cause other DNA disruption except adducts like strand cross-links, breakages and deletions. Some important chemical agents are; tobacco-specific N-nitrosamine, benzidine, aromatic amines, asbestos, benzene, aflatoxins, polycyclic aromatic hydrocarbons (Poirier, 2004, Loeb & Harris, 2008).

Aflatoxins are toxic metabolites of fungi and are carcinogenic in several animal species though with variable potency (CJ Chen & DS Chen, 2002, Zhang, 2010). Aflatoxin B1 (AFB1) which is a very toxic Aflatoxin type is a secondary metabolite of Aspergillus flavus and Aspergillus parasiticus and is known to be a human hepatocarcinogen (Zhang, 2010, Wogan & Newberne, 1967, Wogan, 1976, 1987, 1992). It may contaminate various food resources, which include but is not limited to, cereals such as rice, wheat and maize, as well as corn and peanuts which are stored in warm and humid places (Zhang, 2010, Wogan, 1976, Toteja et al., 2006, Matumba et al., 2009). AFB1 forms DNA adducts with guanine in the DNA of human hepatocytes and is thought to cause G: C to T: A transversion mutations, that acts as a cause of hepatocellular carcinogenesis (Hussain et al., 2007)

2. DNA repair mechanisms

In response to genotoxic stress, which can be mainly caused by various chemicals, reactive cellular metabolites and ionizing or UV radiation, DNA repair pathways and cell cycle checkpoints can be activated, allowing the cell to repair or prevent the transmission of damaged or incompletely replicated chromosomes. The balance between cell cycle arrest, DNA repair and the initiation of cell death could determine if DNA damage is compatible with cell survival or requires elimination of the cell by apoptosis. Defects of DNA repair pathways and cell cycle checkpoints may cause susceptibility to DNA damage, genomic defects, hypersensitivity to cellular stress and resistance to apoptosis, which characterize cancer cells (Ishikawa et al., 2006).

Major DNA repair pathways are base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombinational repair (HR) and non-homologous end joining repair (NHEJ). These pathways each require a number of proteins and enzymes. By contrast, the direct removal of small alkyl groups (such as methyl groups) specifically from the O^6 position of guanine and the O^4 position of thymine in DNA is produced by the action of a single enzyme, O^6-methylguanine-DNA methyltransferase (MGMT) (Fleck & Nielsen, 2004).

2.1 Base excision repair (BER)

BER is characterized by the excision of nucleic acid base residues in the free form (Friedberg et al., 1995). Conversely, NER removes damaged nucleotides which are approximately 30 nucleotides long. The primary and initiating event of BER is the hydrolysis of the N-glycosyl bond, therefore releasing the free base. This hydrolysis in DNA is catalyzed by a class of enzymes called DNA glycosylases (Fiedberg & Wood, 1996).

BER principally repairs non-bulky lesions produced by oxidation, alkylation or deamination of bases. Cells contain various DNA glycosylases, each of them showing a specific substrate spectrum. After hydrolysis of the N-glycosylic bond by a DNA glycosylase, the damaged base is released and an apurinic or apyrimidinic site (AP site) is produced. An AP site can also form spontaneously and represents damage itself (Fleck & Nielsen, 2004). The repair of base loss in these sites utilizes a specific class of endonucleases designated as AP endonucleases. APE1 is the major human AP endonuclease (Friedberg et al., 1995). Two

pathways can repair the AP site formed by a DNA glycosylase: These are short-patch BER (SP-BER) and long-patch BER (LP-BER) pathways. SP-BER involves a single nucleotide replacement followed by ligation (Hoeijmakers, 2001). DNA ligase III interacts with XRCC1, Polβ and poly(ADP-ribose) polymerase-1(PARP-1) and is involved only in short-patch BER (Kubota et al., 1996). LP-BER involves DNA synthesis of multiple nucleotides (usually 2–6 nucleotides) (Hoeijmakers, 2001). The LP-BER depends on factors which are normally involved in DNA replication: DNA polymerase δ (POLδ) or ε (POLε), proliferating cell nuclear antigen (PCNA) and replication factor C (RFC) (Izumi et al., 2003; Sung & Demple, 2006). In LP-BER, the replaced strand does not exposed to degradation during polymerization but rather is displaced and cut away by DNAase IV or flap endonuclease 1 (FEN1), whereas the ligation step is performed by Ligase I (LIG1). LP-BER is usually used in yeast cells whereas SP-BER is generally used in mammalian cells (Altieri et al., 2008).

2.2 Nucleotide excision repair (NER)

NER mainly repairs bulky DNA adducts, such as UV-light-induced photolesions [(6-4) photoproducts (6-4PPs) and cyclobutane pyrimidine dimers (CPDs)], intrastrand cross-links, large chemical adducts generated from exposure to aflatoxine, benzo[*a*]pyrene and other genotoxic agents (Christmann et al, 2003). The names of many of the genes found in NER, start with the letters "XP," because they were first identified in human DNA-repair disease, Xeroderma pigmentosum (XP) (Altieri et al., 2008). NER consists of two repair subpathways: Global genome repair (GGR) and transcription-coupled repair (TCR). GGR removes damage in the whole genome whereas TCR specifically repairs the transcribed strand of active genes (Fleck & Nielsen, 2004).

2.2.1 Global genome repair (GGR)

The XPC/HR23B is the first NER factor to detect a lesion and recruit the repair machinery to the damaged site in GGR (Kusumoto et al., 2001). Another factor which participates the recognition of the damage is UV-DDB (UV-damaged–DNA-binding protein), consisting of two proteins, DDB1 and DDB2 (also known as XPE) (Altieri et al., 2008). The transcription factor transcription factor IIH (TFIIH) is also recruited to the site of DNA damage (Yokoi et al., 2000). The binding of TFIIH is mediated by its p62 subunit which specifically interacts with XPC/HR23B, thus allowing the recruitment of TFIIH to the damaged site (Altieri et al., 2008). TFIIH harbors DNA helicase activity, which is exerted by its helicase subunits XPB and XPD (Schaeffer et al., 1993; Schaeffer et al., 1994). It is responsible for unwinding of DNA around the lesion (Evans et al., 1997a). Except the unwinding function, it is also responsible for the recruitment of XPA and XPG. The initial unwinding by XPB helicase opens up a small region and permits access of XPA to the damaged region. XPA also interacts with many other NER components like TFIIH, RPA and ERCC. The binding of XPA to TFIIH allows the complete unwinding of DNA helix to generate an open stretch of approximately 20-30 nucleotides, with the action of RPA. RPA is the major single-stranded DNA-binding protein required for eukaryotic metabolism. It is involved in many processes like DNA repair, replication, and recombination. RPA facilitates DNA unwinding by TFIIH through its ssDNA binding activity. After the interaction with XPA, RPA binds to the single, undamaged strand thus protecting it from nuclease attack (Lee et al., 2003). After binding of RPA and XPA, XPC/HR23B is released, allowing its recycling for other damaged sites where the repair mechanism must start (Altieri et al., 2008). After damage recognition and the formation of an open complex, removal of the lesion is performed by bidirectional incisions at determined positions flanking the DNA

damage (Evans et al., 1997b). 3'-incision is carried out by XPG (O'Donovan et al., 1994), and 5'-incision is performed by the XPF–ERCC1 complex (Sijbers et al., 1996). The arising DNA gap is filled in by the action of Polδ and Polε and sealed by DNA ligase I and accessory factors (Araujo et al., 2000; Mu et al., 1995).

2.2.2 Transcription-coupled repair (TCR)

Transcription-coupled repair (TCR) is specifically removes DNA lesions in the genomic region where transcription is occurring simultaneously. Nowadays, it is not very clear how repair is coupled with active transcription, but it is generally supposed that a stalled transcript provides a strong signal to attract the repair mechanism. In this situation, the recognition factors intercede the dissociation of RNA polymerase II (RNAPII) from the DNA strand to allow the repair process to continue (Sarasin & Stary, 2007). Slow removal of DNA lesions from transcription templates would prevent efficient transcription. XPB, XPD (as part of TFIIH), XPG, CSA and CSB are essential for TCR (Le Page et al., 2000; Schaeffer et al., 1993). The reduction of transcription in CSB cells upon UV irradiation is caused by blockage of RNAPII at the photoproduct regions (Selby et al., 1997). When RNAPII is inactivated at the site of DNA lesions, CSA and CSB mediate the activation of NER pathway by release of the stalled RNAPII elongation complex from the damaged DNA. GGR and TCR could be related through a direct interaction of CSB and XPG (Iyer et al., 1996). In humans, TCR requires all the proteins needed for GCR except XPC, XPE and HR23B. The following steps of TCR are actually the same as for GCR with the development of the open complex and the lesion demarcation by XPA, RPA, and TFIIH, the excision of damaged strand, the filling by DNA polymerase, and the sealing of DNA fragments by a DNA ligase (Altieri et al., 2008).

2.3 Mismatch repair (MMR)

MMR is a type of DNA repair mechanism that targets base substitution and insertion/deletion mismatches resulting from errors formed during DNA replication and escaped from the proofreading activity of DNA polymerases, an event occurring with a frequency of approximately 1 in 10^9–10^{10} base pairs per cell division (Iyer et al., 2006). It is responsible for removal of these base mismatches which are caused by spontaneous and induced base deamination, methylation, oxidation and replication errors (Christmann et al., 2003).

MMR is well understood in *E. coli*, where the core enzymes of the repair system are the products of the mutH, mutL, and mutS genes. MMR can only protect cells from permanent mutations if the parental strand which contains the correct information can be accurately separated from the daughter strand. In *E. coli*, the strand discrimination signal is achieved by adenine methylation in GATC sequences. Newly replicated DNA is not still methylated on the daughter strand (Modrich, 1991; Friedberg et al., 1995). Thus MutH recognizes the temporarily unmethylated newly synthesized DNA strand and cleaves it at hemimethylated GATC sites which are located within 1,000 bp of the mismatch (Altieri et al., 2008). MutL protein mediates communication between the bound MutH and MutS products (Modrich, 1991). MutL also recruits UvrD at the damage site (Altieri et al., 2008). UvrD helicase and RPA generates a ssDNA filament containing the mismatched base, which is then cleaved by nuclease activities. Ultimately, DNA polymerase III refills the gap truly and DNA ligase III seals the last nick (Kunkel & Erie, 2005).

All eukaryotic organisms have MutS and MutL homologues, MSHs and MLHs, respectively. Five MSHs (MSH2–MSH6) are present in both yeast and mammals, whereas MSH1 exists

only in yeast. MSH2 is required for all mismatch correction in nuclear DNA, whereas MSH3 and MSH6 are required for the repair of some distinct types of mismatched DNA during replication. MSH4 and MSH5 are probably involved in meiotic recombination. Mammalian cells have two MutS activities that function as heterodimers and share MSH2 as a common subunit: MutS*α* (MSH2–MSH6 heterodimer) and MutS*β* (MSH2–MSH3 heterodimer) (Jascur & Boland, 2006; Modrich, 2006). Eukaryotic cell does not contain MutH protein. In this situation the problem is to find an entry point for the strand excision activities. The solution seems to rely on using nicks or gaps left behind by the progressing replication forks, which may explain the respective role of PCNA in MMR (Kunkel & Erie, 2005). Finally, the excision of the DNA strand which contains the mispaired base is carried out by exonuclease I (Genschel et al., 2002) and the new synthesis by Polδ (Longley et al., 1997).

2.4 Double strand break repair (DSBR)

DNA DSBs are the most damaging lesions in the genome. They can form as a result of several damaging agents including ionizing radiation (IR) or chemical exposure (Ataian & Krebs, 2006). The major difference between DSBs and many other types of DNA lesions, including SSBs, is that in DSBs both DNA strands are damaged, which impedes the use of the complementary strand as template in the repair process (Genovese et al., 2006).

The two major pathways used by cells to repair DNA DSBs are homologous recombination (HR) and non-homologous end-joining (NHEJ). HR is an error-free pathway which is usually found in simple eukaryotes (Cromie et al., 2001). Conversely, NHEJ is an error-prone pathway which is usually predominates in mammals (Dasika et al., 1999).

2.4.1 Homologous recombinational repair (HR)

HR is initiated by a nucleolytic excision of the DSB in the 5'–3' direction by the MRE11–RAD50–NBS1 (MRN) complex (Christmann et al., 2003). In the development of MRN complex, MRE11 and RAD50 produce the core complex and then they interact with NBS1. MRE11 has got various biochemical properties, such as DNA exonuclease activity, which can be stimulated by RAD50, DNA unwinding activity and single-strand DNA endonuclease activity. Contribution of MRN complex to DSB sites is supported by the binding of NBS1 to phosphorylated histone-H2AX. After DNA strand excision and protein binding, heteroduplex DNA is formed. This process requires BRCA2 and RAD51. BRCA2 is assigned in controlling the recombinase activity of RAD51 and its loading onto single-stranded DNA (Altieri et al., 2008). RAD51 is assisted by a number of protein factors including RAD52, RAD54, BRCA1 and RAD51 prologues (Rad51B, Rad51C, Rad51D, XRCC2, XRCC3) (Fleck & Nielsen, 2004). Afterwards the resulting 3' single-stranded DNA is bound by a heptameric ring complex formed by RAD52 proteins (Stasiak et al., 2000), which protects against exonucleolytic digestion. For binding of DNA ends, RAD52 competes with the Ku complex. This situation may determine whether the DSB is repaired by the HR or the NHEJ pathway (Van Dyck et al., 1999). RPA is another important protein that interacts with RAD51 (Golub et al., 1998). Interaction of RAD51 with RPA stabilizes RAD51-mediated DNA pairing by binding to the displaced DNA strand (Eggler et al., 2002). Thus, RAD51 catalyzes strand-exchange process with the complementary strand in which the damaged DNA invades the undamaged DNA duplex, displacing one strand as D-loop (Baumann & West, 1997; Gupta et al., 1998). After D-loop formation, the annealed 3'-end is then extended by repair synthesis through the original break site to restore the missing sequence

information at the break point. The sister chromatid provides a proper template for such error-free repair synthesis, actually it is the preferred template for homology-directed repair. On the other side of the D-loop, an "X" like structure, known as Holliday junction, is formed at the border between hetero- and homoduplex. If the Holliday junction is transported in the same direction as replication, it will release strand which is newly synthesized. Once repair synthesis is complete, the next step is to release the newly synthesized end, which can be performed by sliding the Holliday junction toward the 3'-end. Then the two broken ends reconnect. This process is facilitated by RAD52 and promoted by the annealing of complementary sequences. This process may generate gaps or flaps, depending on the degree of 3'-end extension during repair synthesis. Flaps can be removed by XPF/ERCC1 complex also remaining gaps are filled and sealed by PCNA-dependent DNA polymerase δ/ε and DNA ligase I (Altieri et al., 2008).

2.4.2 Non-homologous end joining repair (NHEJ)

The term "non-homologous" is used to describe this repair pathway. Also in this pathway 1–6 bp region of sequence homology (microhomology) near the DNA end frequently facilitates rejoining (Helleday et al., 2007). In contrast to NHEJ, HR is directed by longer stretches of homology (>100 bp) therefore the major difference between NHEJ and HR is the span of homologous sequences associated with repair process (Altieri et al., 2008).

In the first step heterodimeric complex consisting of the proteins Ku70 (Reeves & Sthoeger, 1989) and Ku80 binds to the damaged DNA, thus protecting the DNA from exonuclease digestion (Altieri et al., 2008). Then the DNA–Ku complex attracts and activates the catalytic subunit (DNA-PKcs), a serine/threonine protein kinase. DNA-PKcs is autophosphorylated after juxtaposition of the two DNA ends (Helleday et al., 2007). If further processing of ends is not required, the complex attracts the additional core components, XRCC4, LIG4 and XLF, which together form the ligase complex and seal the DNA ends. In the presence of 3'- and 5'-overhangs, hairpins, gaps and flaps, characterized by single-strand/double-strand transitions DNA end joining requires an additional end processing before sealing (Altieri et al., 2008). Processing of DSBs is mainly performed by the MRN complex (Nelms et al., 1998) which has endonuclease, exonuclease, and helicase activity (Paull and Gellert, 1999) and removes excess DNA at 3' flaps. Flap endonuclease 1 (FEN1) is one of the candidate responsible for removal of 5' flaps (Wu et al., 1999). Other factors which are needed for processing includes structure-specific Artemis nuclease and/or the DNA polymerases POLμ, POLλ, and TdT (Altieri et al., 2008). Artemis acts in a complex with DNA–PK (Moshous et al., 2001). It also displays single-strand-specific exonuclease activity (Ma, 2002). In this process, Ku heterodimer interact with Artemis, and the LIG4/XRCC4 complex, thus organizing the activities and the reversible interaction of the processing factors with the core components (Altieri et al., 2008).

3. Cell cycle checkpoints

Cell cycle checkpoint signaling is activated in response to incomplete DNA replication due to DNA damages induced by both internal and external sources such as UV light, reactive oxygen species, ionizing radiation or DNA damaging chemotherapeutic agents. Active checkpoints prevent further progression during the cell cycle. If the genotoxic stress exceeds repair capacity, additional signaling pathways may cause cell death, probably via apoptosis. (Reinhardt & Yaffe, 2009b). If the damage level is low, the cell can deal with the lesions so it

does not need to activate the checkpoint signaling. If the lesions are not rapidly repairable or if damage level is high, checkpoint signaling mechanisms take place for cell survival and protection of genome integrity (Lazzaro et al., 2009). Cells can arrest at cell cycle checkpoints to allow for: (1) repairing of cellular damage; (2) the dissipation of an exogenous cellular stress signal; or (3) availability of required hormones, growth factors or nutrients (Pientepol & Stewart, 2002). Thus cell cycle checkpoints provide more time for repair of DNA damage before DNA replication and mitosis (Kaufmann & Paules, 1996).

3.1 G_1/S checkpoint

In the presence of DNA damage, the G_1/S checkpoint prevents replication of damaged DNA through two different signal transduction pathways. The first pathway involves the degradation of Cdc25A phosphatase. Chk2 and Chk1 activated by ATM and ATR phosphorylate Cdc25A, which is then degraded by the ubiquitin proteasome pathway (Shimada & Nakanishi, 2006). Cdc25A degradation results from the inactivation of Cdk2 and prevents Cdc45 from loading onto chromatin (Arata et al., 2000). Cdc45 is required for the recruitment of DNA polymerase α, thus lack of Cdc45 incorporation into the chromatin structure inhibits new origin firing. This pathway plays a role in the initial G_1/S checkpoint arrest. In order to maintain this arrest, transcriptional responses are mediated by p53 (Shimada & Nakanishi, 2006). ATM and ATR phosphorylate p53 at Ser15 (Banin et al, 1998; Canman et al, 1998), which inhibits the interaction of p53 with MDM2 (Shieh, 1997), thus p53 is stabilized. ATM also phosphorylates MDM2 on Ser395 and decreases the probability of an interaction between MDM2 and p53, thus p53 is accumulated (Maya et al., 2001) Stabilization and increased transactivation activity of p53 leads to the induction of p21, which inhibits the Cdk2–cyclin E–PCNA complex, thereby inhibiting G_1/S transition (Mailand et al., 2000). p21 also binds to the cyclin D–Cdk4 complex and prevents it from phosphorylating Rb, thus suppressing the Rb/E2F pathway (Nakanishi et al., 2006). Therefore, degradation of cyclin D1 which is a subunit of the cyclin-dependent kinase cdk4, is the critical step in promoting a rapid arrest in G_1. When cyclin D1 disappears, p21 is released from cdk4 complexes and binds rather than cdk2 complexes, preventing progression of cell cycle from G_1 into S phase (Walworth, 2000). In summary, the G_1/S checkpoint response targets two independent and critical tumor suppressor pathways, p53 and pRb, which are most commonly deregulated in cancers (Nakanishi et al., 2006)

3.2 S phase checkpoint

In the S phase, genotoxic stress can arise from DNA-damaging insults or from difficulties with the replication process. S-phase checkpoints are catergorized into three types: (1) the replication-dependent intra-S-phase checkpoint (commonly named as replication checkpoint); (2) the replication-independent intra-S-phase checkpoint (generally named as intra-S-phase checkpoint), which can be induced by double strand breaks; and (3) the S-M checkpoint, which is also depends on DNA replication (Bartek et al., 2004). In the initiation of DNA damage checkpoints activity, the first step is the recognition of DNA damage. Studies in yeasts and mammals have demonstrated that RAD9, RAD1, HUS1 and RAD17 are required factors that activate checkpoint signaling (Melo & Toczyski, 2002). RAD9, RAD1 and HUS1 form a heterotrimeric complex which is known as 9-1-1 complex. RAD17 interacts with four small RFC subunits (Rfc2, Rfc3, Rfc4 and Rfc5) to form an RFC-related complex. When DNA is damaged, the 9-1-1 complex is recruited to the damage site under

the regulation of the RAD17 complex (Melo et al., 2001). In this process chromatin-bound 9-1-1 complex facilitates phosphorylation mediated by ATR and ATM (Nakanishi et al., 2006). During the S-phase, damaged DNA inhibits replicative DNA synthesis (intra-S checkpoint). This checkpoint is regulated by two distinct pathways, known as ATM/ATR–Chk1/Chk2–Cdc25A and ATM–NBS1–SMC1 (Falck et al., 2002). Depending on the type of DNA damage, ATM or ATR phosphorylates Chk2 or Chk1, respectively, resulting in the phosphorylation and degradation of Cdc25A (Shimada & Nakanishi, 2006). Downregulation of Cdc25A subsequently causes inactivation of the S-phase-promoting cyclin E/Cdk2 and prevents loading of Cdc45 on replication origins. The phosphorylation of NBS1 on S343 by ATM is required for activation of the MRN complex and the intra-S checkpoint (Lim et al., 2000; Zhao et al., 2000). Depending on the phosphorylation state of NBS1, SMC1 is phosphorylated on Ser-957 and Ser-966 by ATM which is required for the intra-S checkpoint (Kim et al., 2002; Yazdi et al., 2002). Other mediator proteins, such as 53BP1, BRCA1 and MDC1, are also involved in the intra-S checkpoint by regulating the phosphorylation of downstream proteins such as Chk1, Chk2, and NBS1 (Shimada & Nakanishi, 2006).

3.3 G_2/M checkpoint

The G_2/M checkpoint prevents cells from entry into mitosis through the inhibition of cyclinB/Cdc2 kinase by Chk1/Chk2, p38-mediated subcellular sequestration, degradation, and inhibition of the Cdc25 family of phosphatases. The initiation of G_2/M arrest is also carried out with p53 (Shimada & Nakanishi, 2006). After DNA damage, members of the PI-3K family initiate signal transduction pathways that regulate DNA repair and cell cycle progression. Various members of the PI-3K family can directly phosphorylate p53, including DNA-PK, ATM, and ATR. ATM-dependent signaling also results in activation of the Chk1 and Chk2 kinases (Pientepol & Stewart, 2002). Following DNA damage, the ATM–Chk2–Cdc25A and/or the ATR–Chk1–Cdc25A pathways are activated. 53BP1, MDC1, BRCA1 also play roles in the activation of Chk1 and Chk2 (Chan et al., 1999). MDC1 functions as a molecular bridge between histone γ-H2AX and NBS1 in the MRN complex (Nakanishi et al., 2006). Phosphorylated Cdc25A cause the degradation and inactivation of cyclinB/Cdc2. Many studies suggest that Chk1 and Chk2-mediated phosphorylation of p53 may be a crucial role for stabilization of the protein after DNA damage (Hirao et al., 2000; Shieh et al., 2000). The major targets of p53 at G_2/M checkpoint are the Cdk inhibitor p21, GADD45, which causes the dissociation of the Cdc2 and cyclin complex, and 14-3-3 sigma, which sequesters the cyclin B/Cdc2 complex in the cytoplasm (Chan et al., 1999). Two isoforms of MAP kinase, p38 α and γ are also implicated in the G_2/M checkpoint by the regulation of Cdc25B and Chk2, respectively. Cells which require these genes and enzymes exhibit a G_2/M checkpoint defect (Shimada & Nakanishi, 2006).

4. Polymorphisms of DNA repair genes

Many of the hereditary diseases with cancer predisposition are known to be caused by germ-line mutations of DNA repair genes (Paz-Elizur et al, 2008, Au, 2006). DNA repair deficiencies are milder in sporadic cancers than hereditary cases because of absence of germ-line mutations (Paz-Elizur et al, 2008). Generally, the response to DNA damage involves expression of various genes to repair. Susceptibility to the diseases caused by failure of DNA repair can depend on rare mutations in genes involved in DNA repair or on low penetrance single nucleotide polymorphisms (SNPs) (Ripperger et al., 2009). Although no

clinical decisions can be based on their presence or absence, polymorphisms of DNA repair-related genes may modulate cancer predisposition (Mocellin et al., 2009). SNPs occur when a single nucleotide in the genome sequence is altered; they occur every 100–300 bases along the 3 billion base human genome, so they contain about 90% of all human genetic variations that are thought to account for many health-related conditions, such as individualized drug responsiveness and disease predispositions including cancer (Mocellin et al., 2009, Paz-Elizur et al, 2008). Even though risks conferred by individual loci are relatively small, some risky alleles have been thought to act multiplicatively (Ripperger et al., 2009).

There are several different loci studied for various kinds of diseases and cancers. Cell cycle check-point and DNA repair gene polymorphisms are main foci in those studies.

8-oxoguanine formation is one of the major mutagenic oxidative DNA lesions, frequently used as a measure of oxidative stress. To protect DNA from such a damage, prevention, repair or proofreading must be operated; prevention is by avoiding the incorporation by the enzyme MTH1 to hydrolyse 8-oxo-dGTP; repair is by excising 8-oxoguanine from DNA by OGG1-initiated BER; and proofreading is by removing an adenine misincorporated opposite a template 8-oxoG by MUTYH-initiated BER in order to enable conversion of the premutagenic 8-oxoG:A mispair into a 8-oxoG:C base pair. BER is applied on oxoguanine primarily by 8-oxoguanine DNA glycosylase 1 (OGG1). The most common SNP studied in this gene is *OGG1*Ser326Cys thought to change the phosphorylation status of the enzyme. Studies on polymorphism in this gene region and others involved in BER of oxidative DNA damage, such as *APE1* or *XRCC1*, concluded no associations with cancer risk (Paz-Elizur et al, 2008). XRCC does not related to their biochemical functions; these genes only represent components of different damage recovery pathways (Basso et al., 2007). SSBs can be repaired by PARPs and XRCC1 (Basso et al., 2007, Ladiges, 2006). XRCC1 is known to have a large number of SNPs with its relative high frequency in the population (Basso et al., 2007, Au , 2006, Ladiges, 2006). XRCC1 has no enzymatic activity, but has three interactive domains: the N-terminal domain (NTD) is the site for POL b binding and also the site for direct binding to gapped or nicked DNA. Previously, 27 gene variations of XRCC1 were detected, the most frequent ones are R399Q and R194W (Ladiges, 2006). The XRCC1 194W allele was recently found to have a protective role against tobacco-related cancers. And the XRCC1 399Q allele was shown to behave as a risk factor for tobacco-related cancers in light smokers, but as a protective factor in heavy smokers (Basso et al., 2007).

The Xeroderma pigmentosum complementation group C (XPC) is one of the eight genes in the NER pathway; the others are ERCC1, XPA, XPB, XPD, XPE, XPF and XPG. XPC is involved in the DNA damage recognition and DNA repair initiation in the NER pathway, this is important because the binding of XPC to damaged DNA is the rate-limiting step of NER. Normal XPC gene is found to be critical for the cells to complete excision repair of bulky DNA lesions including smoking-induced DNA adducts. The results of studies about the association of XPC polymorphisms with cancer risk are contradicting (Qui et al., 2008)

XPD gene product is the adenosine triphosphate-dependent DNA helicase component of the transcription factor, TFIIH. The defects in XPD/ERCC2 (the xeroderma pigmentosum group D (*XPD*) gene, also called the excision repair cross-complementing rodent repair deficiency group 2 (*ERCC2*) gene) are the cause of an autosomal recessive skin disorder characterized by solar hypersensitivity of the skin exposed to direct sunlight and so it has high risk for developing epithelial cancers and melanoma (Mocellin et al., 2009, Manuguerra et al., 2006). XPD/ERCC2 is thought to be associated with the likelihood of harboring melanoma. The XRCC3 protein is important in DNA DSBs/recombinational repair as a member of Rad51-

related protein family that is participating in HR to maintain chromosome stability and repair DNA damage (Manuguerra et al., 2006).

Breast cancer is the most common malignancy in women with an average lifetime risk of 8–10%. Breast cancer risk doubles in the women with a first degree relative with the same problem (Ripperger et al., 2009). Germline BRCA1 or BRCA2 mutations account for 20–40% of breast cancer in families, and they are associated with a high lifetime risk of 60–85% for breast cancer as well as an increased risk for ovarian cancer (Ripperger et al., 2009, Basso et al., 2007). In high risk families, some other genes are investigated to find their risk usually concentrating on genes involved in DNA repair as CHEK2, RAD50, BRIP1 and PALB2. Cell cycle checkpoint kinase 2 (CHEK2) is a signalling component of DNA repair phosphorylating BRCA1. Currently, there are several different SNPs in genes or chromosomal loci that have been identified in genome-wide association studies and a common SNP in CASP8 was found to reduce breast cancer risk (Ripperger et al., 2009).

Breast cancer cells are thought to be deficient in DSB repair (Ralhan et al., 2007). The products of key breast cancer susceptibility genes, BRCA1, BRCA2 (XRCC11), ATM and TP53, play important roles in DSB repair and chromosome stability (Ralhan et al., 2007, Basso et al., 2007). ATM mutation (7271T→G) has been suspected to be associated with an increased risk of breast cancer in relatives. The active ATM monomers phosphorylate various DSB repair and genome surveillance factors such as Artemis, NBS1, BRCA1, Fanconi anemia complementation group D2 protein (FANCD2), p53, p53-binding protein 1 (53BP1). Recently RAD50 germline mutations have been related to breast cancer susceptibility. P53 has several responses simultaneously, modulating DNA repair, blocking the cell cycle or inducing apoptosis in irrepairably damaged cells. It inhibits strand exchange mediated by RAD51, binds Holliday junctions and detects mispairings in heteroduplex junction DNA (Ralhan et al., 2007).

The polymorphism studies are usually focused on cancer cases. Since the development of cancer involves the induction of multiple mutations, recent investigations are usually about the interactions of multiple susceptibility genes. But cancer is polygenic and single genetic variants are usually insufficient to predict risk of cancer. Consequently, the functional significance of these SNPs is still largely unknown. Using established common cancer susceptibility SNPs, there are hundreds of possible combinations of genotypes for each kinds of cancer in different populations. The studies for SNPs must be enlarged for various populations to be reliable.

5. DNA repair disorders

DNA repair disorders are usually characterized by X-ray sensitivity, cancer susceptibility, immunodeficiency, neurological abnormalities. DNA repair disorders can be in either of the repair types. Defects in the NER mechanism are responsible for several genetic disorders, including XP (hypersensitivity to sunlight/UV, resulting in increased skin cancer incidence and premature aging), Cockayne syndrome (hypersensitivity to UV and chemical agents), Trichothiodystrophy (sensitive skin, brittle hair and nails). The latter two usually accompanies with mental retardation. XP is an autosomal recessive hereditary disease with a prevalence of approximately 1–4 in 10^6 live births characterized by severe predisposition to skin cancer, mainly squamous cell and basal cell carcinoma (Basso et al., 2007, Au, 2006). XP cells are defective in NER and known responsible genes are XP-A to XP-G (Basso et al., 2007).

Other DNA repair disorders include Werner's syndrome with growth retardation and premature aging; Bloom's syndrome with skin hypersensitivity and high incidence of malignancies and Ataxia telangiectasia(Louis–Bar syndrome) (ATM) with sensitivity to some chemicals and ionizing radiation. ATM mutations are found to be responsible for the autosomal recessive disease, ataxia teleangiectasia, characterized by cerebellar ataxia, telangiectases, immune defects and predisposition to various malignancies (Table 1) (Ripperger et al., 2009). The most common DSB repair defects result from deficiencies in the ATM and NBS genes. The defects in NBS and DNA Ligase IV genes are chromosomal instability syndromes associated with various chromosomal aberrations and translocations (Nahas & Gatti, 2009). All those diseases are "progeria syndromes" means "accelerated aging diseases" because these patients suffer from aging-related diseases at an abnormally young age, while not manifesting all the symptoms of old age.

Hereditary breast cancer, hereditary colon cancer and Fanconi's anemia are also DNA repair diseases. Hereditary breast and ovarian cancer is the most frequent autosomal dominant disorder associated with mutations in BRCA1 or BRCA2. Additionally, there are several diseases increasing breast cancer risk. For instance, Peutz–Jeghers syndrome, caused by heterozygous germline mutations in STK11, is increasing the risk of breast cancer.It is mainly a polyposis syndrome characterized by melanocytic macules of the lips, digits as well as multiple hamartomatous polyps of gastrointestinal tract. Cowden syndrome is another one characterized by multiple hamartomas in skin, gastrointestinal tract, endometrium, breast and brain and it is associated with an increased breast cancer risk of up to 30–50% by the age of 70 years (Ripperger et al., 2009). Hereditary colon cancer is occuring by another defective DNA repair pathway, MMR, causing the predisposition to cancer. This condition leads to microsatellite instability (MSI) and frameshift mutations (Basso et al., 2007). MSI is also a common finding in colorectal tumors of Lynch syndrome patients (Basso et al., 2007, Ripperger et al., 2009). *MUTYH*-associated polyposis (MAP) is another disease with strong predisposition to a hereditary form of colorectal cancer, germ-line biallelic mutations in the *MUTYH* gene has been found to be responsible (Paz-Elizur et al, 2008). Another interesting disease is Fanconi Anemia, characterized by progressive bone marrow failure and multiple congenital abnormalities, which has been suggested to be caused by defects in coordination of NER, HR and translesional DNA synthesis (TLS). Fanconi anemia can be either autosomal recessive or X-linked recessive cancer susceptibility syndrome (Basso et al., 2007, Nahas & Gatti, 2009). Cells taken from Fanconi anemia patients exhibit hypersensitivity to mitomycin C, the DNA crosslinking agent. This hypersensitivity to cross-linking agents increases the risk to create chromosomal abnormalities. The characteristic feature for cell lines of patients deficient in DNA repair and chromatin maintenance proteins is the increased chromosomal aberration frequency (Nahas & Gatti, 2009). Another syndrome, Li–Fraumeni, is caused by germline TP53 mutations, has a high prevalence in breast cancer, soft tissue sarcomas, leukaemia and brain tumors in young population (Ripperger et al., 2009). There are several different genetic syndromes related to DNA repair, and because of the complexity of the repair pathways, various genes are found to be responsible from each. There are still some DNA repair syndromes without any known defective gene region. The XCIND syndrome comprises the chromosomal instability syndromes, the cancer susceptibility syndromes, the DNA DSB repair disorders, and the some primary immunodeficiencies (Nahas & Gatti, 2009).

SYNDROME	GENE	PRIMARY PATHOGENESIS	PATHWAY	PREDISPOSITION
Ataxia Telangiectasia	ATM	ATM protein kinase	HR, NHEJ	Immunodeficiency, cancer
Fanconi Anemia	Fanconi anemia genes (A, B, C, D1, D2, E, F, G, I, J, L, M), Rad50	Replication Fork/Cell Cycle Checkpoint	Multiple pathways, crosslinking repair	myelofibrosis, leukemia, other cancers
X-linked Agammaglobulinemia (Bruton)	BTK	BTK gene function	NER	Immunodeficiency
Lynch Syndrome (Hereditary non-polyposis colorectal cancer : HNPCC)	MLH1, MSH2, MSH6, PMS1, PMS2	DNA repair/cell cycle checkpoint	MMR	Colon cancer (70-85%) Endometrial carcinoma (50%) Other cancers (15%)
Peutz–Jeghers	STK11 (LKB1)	Cell cycle checkpoint	Multiple pathways	Gastrointestinal hamartomatous polyps, breast cancer, other cancers
SCID -ADA	ADA	Toxicity of deoxyadenosine	NHEJ	Immunodeficiency
SCID-Artemis	artemis	DNA end-joining repair	NHEJ	Immunodeficiency
Xeroderma Pigmentosum	XP-A, XP-B		NER	UV-induced skin cancers
Nijmegen breakage Syndrome	NBS1	Double strand DNA repair	Multiple pathways, DSB cell signalling	İmmunodeficiency, microcephaly, lymphoid malignancy
Multiple colorectal adenomas and carcinomas with no germline APC defect	MUTYH	Base excision repair	BER	İndicating mutations in BER genes are involved in cancer.
Werner's Syndrome	WRN RecQ helicase	Cell cycle checkpoint	HR, TLS	Premature aging, cancer
Bloom's Syndrome	BLM RecQ helicase	Cell cycle checkpoint	HR, TLS	Premature aging, cancer

Table 1. Genetic disorders involved in DNA repair pathways
(Pollard & Gatti, 2009, Howlett et al., 2006, Donahue& Campbell, 2004, Mastrocola&Heinen, 2010, Pichierri et al., 2011, Masai, 2011)

The cause of the most of those XCIND syndromes is not determined, suggesting many new DNA repair proteins have yet to be identified. Advanced researches will determine those and perhaps even new paths of DNA repair. Those diseases are important to be resolved both for their susceptibility for various cancers and their illustrating capacity to understand cancer mechanisms and also aging.

6. DNA repair and cancer therapy

The genome is continually exposed to mutagenic stress from endogenous and exogenous insults that damage DNA (Martin et al., 2008b, Moeller et al., 2009, Liang et al., 2009). DNA repair mechanisms play a central role to overcome these damaging effects and maintain DNA integrity. Deregulation of the DNA repair mechanisms is associated with the development of cancer as well as other diseases (Amir et al., 2010, Megnin-Chanet et al., 2010). DNA damage repair mechanisms are required to prevent cancer. However, incomplete efficiency of these repair mechanisms is also required for genotoxic treatments (i.e. chemotherapy and/or radiotherapy) to achieve cure since DNA repair mechanisms greatly affect the response to cytotoxic treatments (Moeller et al., 2009, Rowe & Glazer, 2010). Most of the anticancer therapies lead to DNA damage to trigger death signals in cancer cells. The efficacy of cancer therapy is extensively influenced by DNA repair capacity. Based on this rationale, inhibitors of DNA repair proteins have been developed in cancer therapy, mostly to potentiate the effects of cytotoxic agents (Martin et al., 2008b).

6.1 DNA repair inhibitors as monotherapy (*Synthetic Lethality*)

When mutation of two genes in isolation is compatible with viability, but simultaneous mutation is lethal, these two genes are synthetically lethal (Martin et al., 2008b, Moeller et al., 2009, Mangerich & Burkle, 2011, Reinhardt et al., 2009a, Rowe & Glazer PM, 2010, Helleday et al., 2008). Accordingly, targeting a gene that is synthetic lethal to a cancer-relevant mutation should kill only malignant cells and preserve normal cells (Mangerich & Burkle, 2011). DNA repair is an ideal target for inhibition in cancer cells as the inhibitors should be exclusively toxic to cancer cells and be associated with minimal adverse effects for patients. Therefore, DNA repair inhibitors have been shown to work as single agents in patients with DNA repair defective tumors. The most remarkable example is the use of PARP inhibitors to treat patients with inherited breast and ovarian cancers that lack wild-type copies of BRCA1 and BRCA2 genes. PARP was discovered in 1963 by Chambon and his group. It is a multifunctional nuclear protein implicated in detection and signaling of DNA strand breaks introduced by oxidative stress, ionizing radiations and cytotoxic agents.
PARP is involved in multiple cellular processes, such as DNA repair and maintenance of genomic integrity, regulation of transcription, epigenetic regulation, chromatin remodeling, death via necrosis and apoptosis, regulation of cellular replication and differentiation, inflammation, regulation of telomerase activity and protein degradation via ubiquitination. (Martin et al., 2008b, Sodhi et al., 2010, Rassool & Tomkinson, 2010, Moeller et al., 2009,).
PARP-1 is the most studied and the founding member of the PARP family. It is a 116 kDa protein having substantially conserved structural and functional organization including an N-terminal double zinc finger DNA-binding domain (DBD), a nuclear localization signal, a central auto modification domain and a C-terminal catalytic domain (Sodhi et al., 2010, Megnin-Chanet et al., 2010, Mangerich & Burkle, 2011). Zinc-finger DBD detects and binds to sites of single-stranded DNA damage. PARP1 utilizes NAD^+ as a substrate and catalyzes

the addition of ADP-ribose polymer side chains to itself, DNA ligase III, DNA polymerase-β, XRCC1, and other repair components, by that means recruiting and regulating the effectors of BER. The presence of PARP1 has been demonstrated to be required for efficient functioning of BER (Kupper JH et al., 1997, Sodhi et al., 2010, Mangerich & Burkle, 2011, Amir et al., 2010, Rowe & Glazer, 2010). Cells with defective BRCA-1 and BRCA-2 become highly dependent on other alternative repair pathways. One of those alternative routes is BER. This repair mechanism help prevent the development of DSBs in order to compensate for the inability of BRCA-mutant cells to repair DSB in an error-free manner. Inhibition of this pathway via PARP1 inhibitors increases the number of unrepaired SSBs, which eventually cause the collapse of the replication fork and produces DSBs. As a result, BRCA-defective cells are hypersensitive to the blockade of BER by the inhibition of PARP1 due to dysfunction of DSB repair. The non-tumor cells are better able to tolerate the PARP inhibition because their HR pathway is intact (Farmer et al., 2005, McCabe et al., 2005, Martin et al., 2008b, Amir et al., 2010, Rowe & Glazer, 2010).

Cells that are defective in recombination-related proteins other than BRCA1 or BRCA2, such as RAD51, RAD54, XRCC2, XRCC3, DSS1, replication protein A1, ATM, ATR, CHK1, CHK2, NBS1 and components of the Fanconi anaemia repair pathway, also show increased sensitivity to PARP inhibition. This suggests that PARP inhibitors might also be used in treating several types of tumors with defects in HR (Bryant et al., 2005, McCabe et al., 2006, Bryant & Helleday, 2006, Helleday et al., 2008).

Several phase I and II trials using PARP inhibitors for patients with breast, ovarian, and a variety of other malignancies are currently under way. Olaparib (AZD2281, KU-0059436, KuDOS Pharmaceuticals/AstraZeneca, Cambridge, UK) shows low toxicity, and there are suggestions of significant antitumor activity, as assessed by radiography and by measurement of tumor biomarkers (Yap et al., 2007, Martin et al., 2008b, Rassool & Tomkinson, 2010, Mangerich & Burkle, 2011, Amir et al., 2010, Rowe & Glazer, 2010, Megnin-Chanet et al., 2010, Helleday et al., 2008). Also, *BSI-201* (BiPar Sciences/Sanofi-aventis, San Francisco, California), *ABT-888* (Abbott Labs, Chicago, IL), *AG-014699* (Agouron Pharmaceuticals/Pfizer Inc., La Jolla, CA), *MK-4827* (Merck & Co Inc, Whitehouse Station, NJ) and *Cep-9722* (Abbott Labs, Chicago, IL) are strong inhibitors of PARP-1 and they are currently undergoing phase I or II testing both as monotherapy as well as in combination with a variety of different chemotherapy regimens.

Another synthetic lethal interaction has been determined between ATM and p53. Loss of ATM or Chk2 strongly increased the sensitivity of p53-deficient cells to doxorubicin-induced cell death. Inhibition of ATM/Chk2 in p53-deficient tumors provides an elegant synthetic lethality-based strategy to sensitize these tumors for DNA-damaging chemotherapy (Reinhardt et al., 2007, 2009a).

The major challenge in the area of synthetic lethal approaches to cancer treatment is the identification of new synthetic lethal pairs. Genome-wide RNAi screening and next generation sequencing of cell lines and primary tumors should allow the systematic search for new synthetic lethal relationships (Rowe & Glazer, 2010).With the exploitation of new synthetic lethal approaches it is possible that novel therapeutics can be identified that show strong selectivity for tumor cells, yield better response rates and lower toxicity.

6.2 DNA repair inhibitors in combination therapy

Several clinical and preclinical studies using PARP inhibitors in combination with cytotoxic agents including alkylating agents, topoisomerase inhibitors, DNA-crosslinking agents and

ionizing radiation (IR) have been conducted. The data showed that PARP inhibitors sensitize malignant cells to all of these agents and to IR. (Martin et al., 2008b, Sodhi et al., 2010, Mangerich & Burkle A, 2011, Rowe & Glazer PM, 2010, Megnin-Chanet et al., 2010, Helleday et al., 2008).

6.2.1 Alkylating agents

Temozolomide (TMZ) is an alkylating agent which is used as a single agent or in combination with IR in the therapy of glioblastoma multiforme and melanomas (Stupp et al., 2005, Mangerich & Burkle, 2011). TMZ can cross the blood brain barrier effectively and display limited bone marrow toxicity (Plummer et al., 2005, Mangerich & Burkle, 2011, Helleday et al., 2008). The therapeutic benefit of TMZ depends on its ability to methylate DNA which occurs mostly at N-7 and O-6 position of guanine residues. TMZ also methylates N-3 position of adenine. This methylation damages DNA and triggers the death of tumor cells. However, some tumor cells show resistance to TMZ by repairing this type of DNA damage and therefore diminish therapeutic efficacy of the drug. Tumor cells express O-6 methylguanine-DNA methyltransferase (MGMT) in response to drug and subsequently repair O6-methylguanine. (Hegi et al., 2005, Martin et al., 2008b, Mangerich & Burkle, 2011, Rowe & Glazer, 2010, Megnin-Chanet et al., 2010). A potent oral inhibitor of MGMT O-6(4bromothenyl) guanine has been used in combination with TMZ with Phase II trials ongoing in metastatic melanoma and colorectal cancer (Hegi et al., 2005). TMZ has been also used in combination with PARP inhibitors due to its mechanism of action. Methylation products of TMZ are repaired efficiently by BER. PARP activity increases after TMZ administration because of DNA damage induction. As PARP inhibition blocks BER, increased cytotoxic lesions become lethal via induction of apoptosis. However, TMZ resistance develops if there is a deficiency in the MMR, which contributes to TMZ cell killing when functional. MMR is required for the induction of DNA strand breaks after the formation of methyl products. PARP inhibitor AG14361 has been indicated to restore sensitivity to TMZ in MMR-deficient human colon and ovarian cancer cells (Curtin N et al., 2004).

6.2.2 Platinium drugs

Cisplatin, carboplatin and oxaliplatin are the most commonly used chemotherapeutic compounds in cancer patients (Helleday et al., 2008). These drugs cause inter- and intrastrand crosslinks that are repaired by NER. It has been suggested that upregulation of ERCC1 expression, is a key enzyme in NER, is associated with the resistance to platinum-based therapy. ERCC1 inhibitors have therefore been developed to deal with the resistance to platinium therapies (Altaha et al., 2004).

Another resistance to platinum drugs develops due to the silencing of MMR genes by hypermethylation. The toxicity of agents such as cisplatin depends on functional MMR. For this reason, DNA demethylating agents such as 2′-deoxy-5-azacytidine (decitabine; MGI Pharma, Bloomington, Minnesota, USA) have been combined with platinum compounds to reverse drug resistance. Preclinical data from xenograft models and translational studies from drug-resistant cells and tissues that are MMR-deficient owing to MLH1 hypermethylation have demonstrated increased chemotherapeutic efficacy when a demethylating agent is combined with platinum chemotherapy (Gifford et al., 2004, Plumb et al., 2000). Decitabine is currently being tested in combination with carboplatin in a phase II clinical trial in patients with ovarian cancer.

PARP1 has a direct role in the repair of damages triggered by platinum compounds. Thus, PARP1 inhibitors potentiate the effect of platinum compounds (Bartsch et al., 2010). PARP-1 inhibitors, in conjunction with platinum derivatives, were found to exhibit significant survival benefit over monotherapy in a relatively small phase II study. In this study, data were reported from a randomized phase II study of combination chemotherapy with carboplatin and gemcitabine with or without PARP1 inhibitor (BSI-201) in patients with triple negative breast cancer (O'Shaughnessy et al., 2009). In combined chemotherapy, PARP-inhibition is highly attractive, as carboplatin will cause DNA strand-breaks while BSI-201 will block PARP1-dependent repair (Bartsch et al., 2010). BSI-201 is currently in phase III clinical trials for breast cancer and squamous cell lung cancer therapy in combination with gemcitabine/carboplatin.

6.2.3 Topoisomerase inhibitors

Topoisomerases are a group of enzymes that resolve torsional strains enforced on the double helix during DNA replication. Topoisomerase 1(Topo 1) induces transient SSBs by forming a covalent DNA-Topo 1 complex (Wang, 2002). Resealing of these breaks restores DNA integrity. (Koster et al., 2007, Pommier, 2006). Camptothecins are the inhibitors of Topo 1 which target Topo 1-DNA intermediate (Pommier, 2006, Waardenburg et al., 2004). Topotecan and irinotecan are the analogs of Camptothecins and they are used as anticancer agents in patients with ovarian, cervical and small cell lung cancer (Pommier, 2006). These inhibitors reversibly stabilize the covalent Topo 1- DNA intermediate by inhibiting DNA relegation. Topo 1-DNA-drug intermediates are converted to lethal lesions due to DSBs during replication (Waardenburg et al., 2004).

PARP1 induces Topo 1 activity in response to DNA damage. Thus, combined therapy of Topo1 inhibitors with PARP1 inhibitors may potentiate cytotoxic effects of Topo 1 inhibitors (Mangerich & Burkle, 2011, Bowman et al., 2001, Delaney et al., 2000).

In vitro combination experiments using platinum compounds with Topo 1 inhibitors showed a synergic effect in various cell lines (Waardenburg et al., 2004).

6.2.4 Ionizing radiation

DNA-dependent protein kinase (DNA-PK) is an essential enzyme in repairing DSBs by NEJ following IR. DNA-PK is a member of phosphatidylinositol-3-kinase (PI3K) superfamily. After cellular exposures, DNA-PK is autophosphorylated, which is crucial for efficient NHEJ. Studies show that cells defective in DNA-PK are highly sensitive to IR which makes it an attractive molecular target for cancer therapies (Collis et al., 2005). Currently, a number of potent and selective DNA-PK inhibitors are available including Vanillin, Su11752, IC87102, IC87361, NU7441, NU7026 and Salvicine (Salles et al., 2006, Hollick et al., 2003, Leahy et al., 2004, Ismail et al., 2004).

PARP1 inhibition might have radiosensitizing effect following IR therapy which creates SSBs and DSBs since its inhibition introduces additional cytotoxicity to tumor cells (Dungey et al., 2008, Noel et al., 2006).

6.2.5 ATM inhibition

Two kinases from (PI3K)-related protein kinase family, ATM and ATR are central to cellular response to DSBs. Once the kinases are activated, many proteins are phosphorylated by ATM and ATR which initiates a cascade inducing cell-cycle arrest and facilitates DNA

repair. ATM inhibition makes tumor cells more sensitive to agents that cause DSBs (Helleday et al., 2008). KU55933, an inhibitor of ATM kinase activity, is currently in preclinical development.

PARP-deficient cells have been shown to be sensitive to KU55933 and NU7026, which is a DNA-PK inhibitor. Based on this data, a relationship between PARP1, ATM and DNA-PK may have value in terms of combination therapy in cancer patients (Bryant & Helleday, 2006).

It now seems likely that an understanding of how DNA damage contributes to tumorigenesis and how this damage is repaired can be used to design novel therapeutic approaches to cancer. In BRCA-associated cancers, the inhibition of BER with agents such as the PARP inhibitors may provide an effective synthetic lethality approach resulting in tumor cell death with minimal toxicity to normal tissues.

Even though the use of PARPi in cancer therapy has received much attention in recent years, some issues remain to be addressed carefully in the near future:

An important question is the issue of long-term safety. A major drawback in the systemic long-term treatment with PARP inhibitors is the damage to DNA repair and genomic stability in normal cells, which may lead to secondary tumors at later age. Basic research into obtaining a more complete picture of all DNA repair pathways and their interplay is crucial for solving the existing problems as well as for the future of DNA repair inhibitors in cancer therapy.

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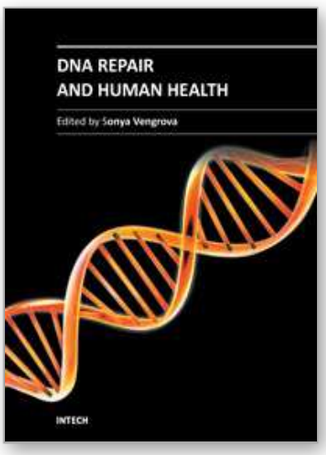

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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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