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# 8

# DNA Repair, Cancer and Cancer Therapy

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## 1. Introduction

The success of an organism to survive from one generation to the next is largely dependent upon the fidelity of replication of its genetic material, deoxyribonucleic acid (DNA). Unfortunately, DNA in living cell is labile and subject to many chemical alterations, and these alterations, if not corrected, can to lead to diseases such as cancer (Fig. 1) (Pallis & Karamouzis, 2010). All eukaryotic cells have evolved a multifaceted response to counteract the potentially deleterious effects of DNA damage (Fig. 2). Upon sensing DNA damage, cell cycle checkpoints are activated to arrest cell cycle progression to allow time for repair before the damage is passed on to the next generation of cells. Depending on the type of damage, other cellular mechanisms such as transcriptional program activation, DNA repair pathways, and apoptosis can also be induced. All of these processes are coordinated so the genetic material is faithfully maintained, duplicated, and segregated within the cell. Important goals of cancer research are to determine the molecular mechanisms that are involved in the formation of genetic changes in human genes as a consequence of DNA mutations and to explain how cancer cells withstand and counteract DNA damage by the use of different defense mechanisms ranging from free radical scavengers to sophisticated DNA repair mechanisms.

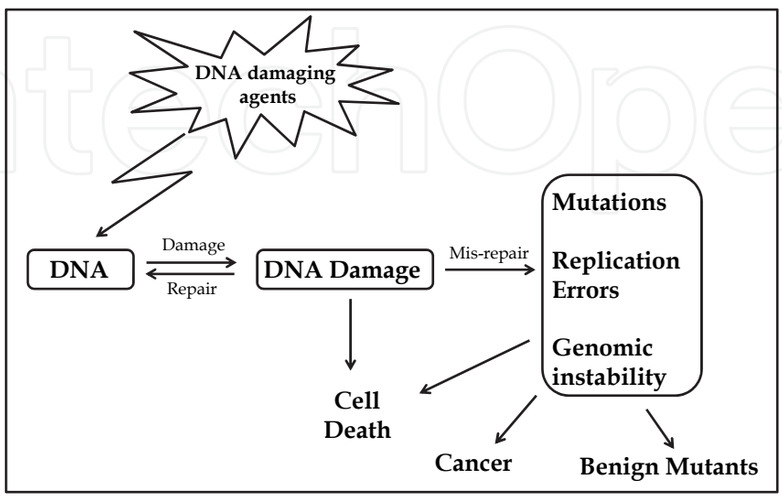


Fig. 1. General pathways linking DNA damage and cancer.

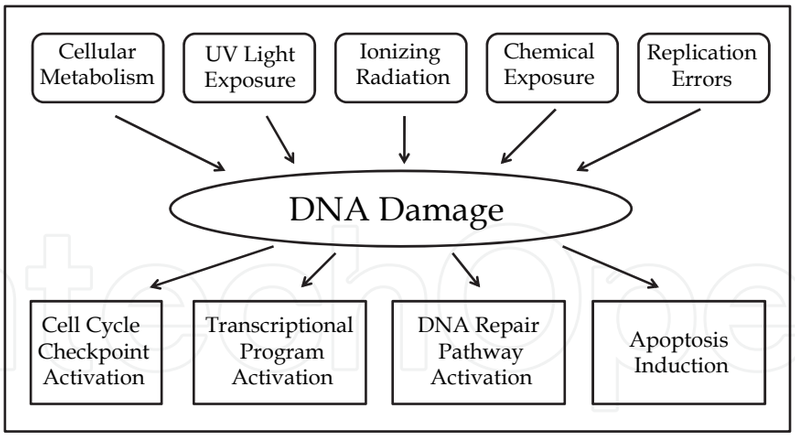


Fig. 2. DNA damage responses. When DNA is damaged by a variety of sources, the cellular response to damage involves activation of multiple processes in order to maintain genomic integrity.

Investigations into the regulation and the effects of DNA repair on tumor survival have expanded very rapidly in recent years. Research on targeting molecular pathways such as angiogenesis, DNA repair, and apoptosis is becoming one of the important areas in clinical oncology. Indeed, many pharmaceutical companies are developing inhibitors against DNA damage response pathways for cancer treatment.

## 2. Overview of DNA repair mechanisms

As a major defense system against DNA damage, DNA repair maintains genome fidelity that is essential to the health of the individual and to the reproductive success of a species. DNA repair is involved in many processes that minimize cell killing, mutations, replication errors, and genomic instability. Abnormalities in these processes have been implicated in cancer and other diseases (Preston et al., 2010). There are at least six different DNA repair pathways in mammalian systems, including base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), non-homologous end-joining (NHEJ), transcriptional-coupled repair (TCR), and mismatch repair (MMR). Disruption in these repair pathways can allow mutations to proliferate, leading to genomic instability. In fact, elevated levels of DNA repair proteins are often seen in drug-resistant tumor cells because a large number of conventional anti-cancer therapies are based on killing cancer cells through inducing DNA damage (Altaha et al., 2004; Drummond et al., 1996; Minn et al., 1995). Our understanding on the damage/errors repaired by each of these pathways has much improved from decades of intense biochemical and molecular genetic studies. Today we know that tumor cells respond differently to DNA damaging agent and their DNA repair activities vary. Thus, therapeutic targeting of specific components of the DNA repair pathways in cancer cells has become one of the major strategies in anti-cancer drug development.

### 2.1 Base excision repair (BER)

The BER pathway repairs base lesions and/or single-strand breaks (SSBs) induced by oxidative and alkylating agents in the DNA template. DNA glycosylases are responsible for initial recognition of the lesion. They flip the damaged base out of the double helix and cleave

the *N*-glycosidic bond of the damaged base, leaving an apurinic/apyrimidinic (AP) site on damaged DNA strand. This site is identical to that generated by spontaneous depyrimidination or depurination. Six DNA glycosylases have been identified in humans to date - each excises an overlapping subset of either spontaneously formed (*e.g.*, hypoxanthine), oxidized (*e.g.*, 8-oxo-guanine), alkylated (*e.g.*, 3-methyladenine), or mismatched bases (Baute & Depicker, 2008). Then the AP endonucleases cleave an AP site to yield a 3′-hydroxyl adjacent to a 5′-deoxyribosephosphate. The resulting gap is subsequently filled by the 5′-deoxyribose-phosphodiesterase action of a DNA polymerase β and the strands are re-ligated by a DNA ligase. Defects in BER genes increase the mutation rate in a variety of organisms. For example, mutations in Pol β have been found in 30% of human cancers, and some of these mutations lead to transformation when expressed in mouse cells (Starcevic et al., 2004). Mutations in the DNA glycosylase MYH are also known to increase susceptibility to colon cancer (Kastrinos & Syngal, 2007).

### 2.2 Nucleotide excision repair (NER)

The NER is the predominant DNA repair pathway by which the cell maintains genomic integrity. It is responsible for removing a wide range of DNA damage, including UV-induced DNA cyclopurine dimers (CPDs), 6-4 photoproducts, and cisplatin induced DNA crosslinks (Ciccia & Elledge, 2010). There are 9 major proteins involved in NER in mammalian cells and their names come from the diseases associated with the deficiencies in those proteins. XPA, XPB, XPC, XPD, XPE, XPF, and XPG all derive from *Xeroderma pigmentosum* (XP) while CSA and CSB represent proteins linked to Cockayne syndrome (CS). In addition, other proteins are also found to participate in NER including ERCC1, RPA, PCNA, RAD23A, and RAD23B. There are four basic steps involved in NER: 1) Damage recognition, 2) Damage demarcation, 3) Incision, and 4) Repair patch synthesis and ligation. Two proteins, XPA and XPC-RAD23B, have been implicated in the damage recognition step, XPE has been shown to have a high affinity for damaged DNA, but whether it is required for the damage recognition step of NER remains unclear. CSA and CSB are mainly involved in the damage recognition step of the transcription-coupled repair. Once the DNA damage is recognized, XPB and XPD, which are subunits of transcription factor TF-IIH and have helicase activity, unwind the DNA at the sites of damages. XPF and ERCC1 form a protein complex which exhibits structure-specific endonuclease activity that is responsible for the 5′ incision during the NER process. The 3′ incision is made by the XPG protein and taken place prior to 5′ incision. The resulting gap in DNA is then filled by DNA polymerases δ and ε. Proliferating cell nuclear antigen (PCNA) assists the DNA polymerases in the reaction, and replication protein A (RPA) protects the other DNA strand from degradation during NER. Finally DNA ligase seals the nicks to finish NER. One good example of targeting NER as an anti-cancer therapy is the use of cisplatin (Altaha et al., 2004; Balin-Gauthier et al., 2008; Prewett et al., 2007).

### 2.3 Homologous recombination (HR)

HR is a type of genetic recombination in which nucleotide sequences are exchanged between two similar or identical DNA molecules. HR is most widely used by cells to repair potentially lethal double-strand breaks in DNA. HR produces new combinations of DNA sequences during meiosis and these new sequences represent genetic variation in offspring, which enables populations to adapt during the course of evolution. Although HR varies

among different organisms and cell types, most forms of HR share the same basic steps. After a double-strand break occurs, sections of DNA around the break on the 5'-end of the damaged chromosome are removed in a process called *resection*. In the *strand invasion* step that follows, an overhanging 3'-end of the damaged chromosome then "invades" an undamaged homologous chromosome. A mobile, cross-shaped intersection of four strands of DNA called a Holliday junction is formed between the two chromosomes after strand invasion. In the pathways of HR involved in DNA repair, a second Holliday junction forms. Depending on how the two junctions are resolved (*e.g.*, cut), the meiotic version of HR results in either chromosomal crossover or non-crossover. HR is also used in horizontal gene transfer to exchange genetic material between different strains and species of bacteria and viruses, and it has been targeted for cancer therapy (Helleday et al., 2005; Litman et al., 2005; Plo et al., 2008).

### 2.4 Non-homologous end-joining (NHEJ)

NHEJ is also a pathway that repairs double-strand breaks in DNA. NHEJ is referred to as "non-homologous" because the break ends are directly ligated without the need for a homologous template, in contrast to HR, which requires a homologous sequence to guide repair (Moore & Haber, 1996). NHEJ typically utilizes short homologous DNA sequences called microhomologies to guide repair. These microhomologies are often present in single-stranded overhangs on the ends of double-strand breaks. When the overhangs are perfectly compatible, NHEJ usually repairs the break accurately (Boulton & Jackson, 1996; Budman & Chu, 2005; Moore & Haber, 1996; Wilson & Lieber, 1999). Imprecise repair leading to loss of nucleotides can also occur, but is much more common when the overhangs are not compatible. Inappropriate NHEJ can lead to translocations and telomere fusion, which are hallmarks of tumor cells (Espejel et al., 2002). NHEJ is evolutionarily conserved throughout all kingdoms of life and is the predominant double-strand break repair pathway in mammalian cells (Guirouilh-Barbat et al., 2004). In budding yeast (*Saccharomyces cerevisiae*), however, HR dominates when the organism is grown under common laboratory conditions.

When the NHEJ pathway is inactivated, double-strand breaks can be repaired by a more error-prone pathway called microhomology-mediated end joining (MMEJ). In this pathway, end resection reveals short microhomologies on either side of the break, which are then aligned to guide repair (McVey & Lee, 2008). This contrasts with classical NHEJ, which typically uses microhomologies already exposed in single-stranded overhangs on the double-strand breaks (DSBs) ends. Repair by MMEJ therefore leads to deletion of the DNA sequence between the microhomologies.

### 2.5 Transcriptional-coupled DNA repair (TCR)

The TCR pathway is an additional NER sub-pathway that allows for the preferential repair of transcription-blocking lesions on the transcribed strand of active genes (Tornaletti, 2009). It operates in tandem with transcription. DNA repair and transcription had long been considered as fully separable processes until recently when several discoveries showed that transcription could be coupled to the selective repair of the transcribed strand (Bohr et al., 1985; Hanawalt et al., 1994; Mellon & Hanawalt, 1989; Mellon et al., 1987). Failure of the TCR is the known cause of Cockayne syndrome (CS), an extreme form of accelerated aging that is fatal early in life (Sarker et al., 2005).

### 2.6 Mismatch repair (MMR)

MMR is primarily responsible for removing unpaired nucleotides. MMR discriminates between two strands so that the newly synthesized 'daughter' strand is repaired to match the 'parent' strand, rather than mutating the 'parent' strand to match the 'daughter' strand. MMR is a highly conserved process. First, MutS forms a dimer (MutS2) to recognize the mismatched base on the 'daughter' strand and binds the mutated DNA (Acharya et al., 2003). MutL then binds the MutS-DNA complex and recruit MutH to the damaged site. MutH subsequently binds and nicks the 'daughter' strand near the mismatched site and and recruit an UvrD helicase (DNA helicase II) to separate the two strands with a specific 3' to 5' polarity. The entire MutSLH complex then slides along the DNA in the direction of the mismatch, librating the strand to be excised as it goes. An exonuclease trails the complex and digests the ssDNA tail. The single-stranded gap created by the exonuclease is filled by DNA polymerase III using the other strand as a template. Finally the nicks are sealed by DNA ligase. Deficiencies in MMR are believed to account for almost all cases of hereditary nonpolyposis colon cancer (HNPCC) and many other cancers such as sporadic colorectal, endometrial, ovarian, gastric, and urothelial cancers, presumably due to the high rate of replication, which leads to the accumulation of DNA mismatches (Sancar, 1999). Mismatched nucleotides may arise from polymerase misincorporation errors, recombination between heteroallelic parental chromosomes, or chemical and physical damage to the DNA (Friedberg et al., 2006). MutS homologs (MSH) and MutL homologs (MLH/PMS) are highly conserved proteins that are essential for the mismatch repair (MMR) excision reaction (Kolodner et al., 2007). In human cells, hMSH2 and hMLH1 are the fundamental components of MMR. The hMSH2 protein forms a heterodimer with hMSH3 or hMSH6 and is required for mismatch/lesion recognition, whereas the hMLH1 protein forms a heterodimer with hMLH3 or hPMS2 and forms a ternary complex with MSH heterodimers to complete the excision repair reaction (Acharya et al., 2003; Kolodner et al., 2007). Human cells contain at least 10-fold more of the hMSH2-hMSH6/hMLH1-hPMS2 complex, which repairs single nucleotide and small insertion-deletion loop (IDL) mismatches, compared with the hMSH2-hMSH3/hMLH1-hMLH3 complex, which primarily repairs large IDL mismatches (Cannavo et al., 2005; Drummond et al., 1997; Raschle et al., 1999). In addition to MMR, the hMSH2-hMSH6/hMLH1-hPMS2 components have also been uniquely shown to recognize lesions in DNA and to signal cell cycle arrest and apoptosis (Fishel, 1999; Fishel, 2001).

## 3. Exploiting DNA damage response defects in cancer

In recent years, it has become evident that DNA damage responses are central for both the development and therapy of cancer. Defects in DNA damage response predispose to cancer by enhancing the accumulation of oncogenic mutations, and these mutations can provoke spontaneous DNA damage that suppresses the evolution of incipient cancer cells. Important goals of cancer research are to understand the molecular mechanisms by which cancers arise and to develop anti-cancer drugs that attack the Achilles' heel of cancer cells. Insight from understanding and targeting DNA damage response pathways has launched a new era in cancer therapy.

### 3.1 BRCA1/BRCA2 deficiencies

Breast cancer is the most common malignancy in women and an estimated 10% of the female population is affected by this disease (Alberg & Helzlsouer, 1997). About 5% of all breast

cancers are ascribed to hereditary predisposition. Extensive research efforts in the early 1990s have led to the identification of two major breast cancer susceptibility genes, *BRCA1* and *BRCA2* (Futreal et al., 1994; Miki et al., 1994; Narod & Foulkes, 2004; Tavtigian et al., 1996; Wooster et al., 1995). Individuals carrying mutations in either one of the alleles will have a life-long high risk for either breast or ovarian cancers (Narod & Foulkes, 2004). Harmful *BRCA1* or *BRCA2* mutations may also increase a woman's risk of developing cervical, uterine, pancreatic, stomach, gallbladder, bile duct, melanoma, and colon cancers (Kadouri et al., 2007; Thompson & Easton, 2002). The likelihood that a breast and/or ovarian cancer is associated with a harmful mutation in *BRCA1* or *BRCA2* is highest in families with a history of multiple cases of breast cancer, cases of both breast and ovarian cancer, one or more family members with two primary cancers. However, it is important to note that most research related to *BRCA1* and *BRCA2* has been carried out on large families with many individuals affected by cancer. Thus, this risk estimate may not apply to general population. To date more than 600 mutations in the *BRCA1* and *BRCA2* genes are known. These mutations can be changes in one or a small number of DNA pairs or large rearrangements of DNA. Mutated BRCA proteins do not function properly. BRCA1 is directly involved in the repair of damaged DNA by interacting with RAD51 to repair breaks in DNA. BRCA2 has a similar function in repairing DNA. Defects in either or both proteins lead to unrepaired DNA damages in other genes. As these defects accumulate, they will allow cells to grow and divide in an uncontrollable manner and eventually form a tumor. Thus, direct or indirect targeting BRCA1 or BRCA2 and their interrelated pathways may have a significant clinical implication. For example, using a gene therapy to restore BRCA1's tumor suppressor function in cancer cells in order to suppress tumor cell proliferation has been demonstrated (Tait et al., 1997). Preclinical and clinical findings indicated that restoration of normal function of BRCA1 could have the therapeutic potential to inhibit tumor growth (Tait et al., 1999).

### 3.2 p53 mutations

p53 is a tumor suppressor protein encoded by the TP53 gene in humans (Isobe et al., 1986; Kern et al., 1991; Matlashewski et al., 1984; McBride et al., 1986). Mutations or inactivation of p53 is a universal feature of human cancers (Storey et al., 1998). As a transcription factor, p53 plays a critical role in apoptosis, genetic stability, and inhibition of angiogenesis (Farnebo et al., 2010; Gaiser et al., 2009; Strachan & Read, 1999). It is normally expressed at low levels so that it does not disrupt the cell cycle or induce the cell to undergo apoptosis. Thus its activity is mainly controlled by regulation of its protein expression levels mediated primarily by the ubiquitin ligase mouse double-minute 2 (MDM2), which targets p53 to the proteasome for degradation (Toledo & Wahl, 2006). It has been demonstrated that p53 becomes activated in response to a variety of stress types including DNA damage, oxidative stress, osmotic shock, ribonucleotide depletion, and deregulated oncogene expression (Han et al., 2008; Hollstein et al., 1991; Tyner et al., 2002). If the TP53 gene is mutated, tumor suppression will be severely reduced. High levels of mutant p53 protein are often observed in tumors (Bartek et al., 1991; Hassan et al., 2008; Iggo et al., 1990; Jonason et al., 1996; Lee et al., 2007; Rotter, 1983). Accumulation of mutant p53 has no correlation with tumor progression, however, it correlates well with increased metastasis (Morton et al., 2010). Previous studies suggest that ~50% of all human tumors overexpress a nonfunctional mutant p53 that accumulate to high concentrations in tumor cells (Brosh & Rotter, 2009; Brown et al., 2009; Nigro et al., 1989). Thus, targeting mutant p53 could be an extremely efficient strategy for selective killing of tumor cells (Mandinova & Lee, 2011).

### 3.3 BRCA-*Fanconi Anemia* (FA) pathway

Over the past few years, study of the rare inherited chromosome instability disorder, *Fanconi Anemia* (FA), has revealed a novel DNA damage response pathway, the BRCA-FA pathway. This pathway consists of *BRCA1*, *BRCA2*, and a network of at least 12 *FA* genes and is commonly inactivated in solid tumors (Thompson, 2005). Functional loss of the BRCA-FA pathway leads to increased cellular sensitivity to DNA damaging agents, defects in cell cycle checkpoints, and cancer predisposition (Litman et al., 2008). While the molecular function of the BRCA-FA protein complex remains unclear, evidence has suggested that the BRCA-FA protein complex is required to mediate the interstrand cross-link (ICL)-induced cellular response (Thompson, 2005). *FA* cells lacking any of the BRCA-FA proteins fail to respond to ICLs, which leads to cellular sensitivity and a prolonged accumulation of cells at the late S or G2/M checkpoint (Litman et al., 2008). Similarly, *BRCA1* mutant cells also fail to respond to ICLs by arresting DNA synthesis and are hypersensitive to ICLs, which causes profound genetic instability (Shen et al., 1998; Xu et al., 1999). Increased cancer risk has been observed in heterozygous carriers of *FA* gene mutations, in particular an increased susceptibility to breast and ovarian cancers (King et al., 2003). These observations suggest that the BRCA-FA pathway is important in the prevention of the female cancers and that unidentified mutations in *FA* genes may account for some familial breast/ovarian cancer pedigrees not accounted for by *BRCA1* or *BRCA2/FANCD1*.

The association between abnormalities in the BRCA-FA pathway and cancer development may have important clinical implications as regards treatment. FA patients who are homozygous for mutation of a *FA* gene have a systemic DNA repair defect that results in a low tolerance for DNA-damaging chemotherapeutic agents. For this reason, chemotherapeutic agents are often given at low dosage or are avoided in favor of surgical approaches for these patients (Kutler et al., 2003). The situation, however, is different for cancer patients who carry a heterozygous mutation in a *FA* gene. In this scenario the tumor contains an abnormal FA pathway and would be predicted to be more DNA damage sensitive whereas the patient's other cells, such as those in the bone marrow, contain a functional pathway and would be relatively more DNA damage resistant. Consistent with this model *BRCA2/FANCD1* mutation carriers, with breast or ovarian cancer, demonstrate a high response to DNA-damaging chemotherapeutic agents (Cass et al., 2003; Chappuis et al., 2002). It remains to be seen if malignancies associated with heterozygosity for other *FA* gene mutations demonstrate the same level of chemo-sensitivity.

### 3.4 ATM/ATR

Ataxia-telangiectasia mutated (ATM) is a serine/threonine protein kinase activated by DNA double-strand breaks (DSBs) (Abraham, 2001). Its activity is increased 2-3 folds in response to DSBs. It phosphorylates several key proteins such as tumor suppressors p53, CHK2, and H2AX that initiate activation of the DNA damage checkpoint, leading to cell cycle arrest, DNA repair or apoptosis. ATM is recruited to DSBs by a trimeric complex of the three proteins MRE11/RAD50/NBS1. ATM directly interacts with the NBS1 subunit and phosphorylates the histone variant H2AX, generating binding sites for adaptor proteins with a BRCT domain. These adaptor proteins then recruit different factors including p53 and CHK2 to repair DSBs. ATM also phosphorylates MDM2 and p53, leading to stabilization and activation of p53 and subsequent transcription of numerous p53 target genes which eventually result in long-term cell-cycle arrest or apoptosis (Morgan, 2007). AT and most of other AT-like disorders are defective in ATM. Since one feature of the ATM

protein is its rapid increase in kinase activity immediately following DSBs, phosphorylating its substrates involved in DNA repair, apoptosis, G1/S, intra-S checkpoint, and G2/M checkpoints, gene regulation, translation initiation, and telomere maintenance (Kurz & Lees-Miller, 2004), a defect in ATM has severe consequences in repairing certain types of DNA damage, and cancer may result from improper DNA repair. For example, both leukemias and lymphomas are found to be associated with ATM defects (Chen, 2000). On the other hand, making ATM dysfunction can be an effective strategy for killing cancer cells. Many specific inhibitors of ATM have thus been developed for the treatment of cancer (Hickson et al., 2004).

The ATM- and Rad3-related (ATR) kinase is highly related to ATM (Abraham, 2001), and occupies a similar proximal position in checkpoint signaling cascades. ATM and ATR appear to phosphorylate many of the same substrates, though their functions are clearly distinct. ATR responds not only to DSBs, but also to damages caused by UV, cisplatin, hydroxyurea (HU), and stalled DNA synthesis (Abraham, 2001). Deficiency in ATR leads to a phenotype resembling mitotic catastrophe, suggesting an essential role for ATR in monitoring DNA replication (Hekmat-Nejad et al., 2000; Michael et al., 2000). ATR is constitutively bound to another protein, the ATR-interacting protein (ATRIP), which acts as a regulatory subunit for ATR. ATRIP cannot bind DNA without ATR and checkpoint activation requires both ATR and ATRIP, and possibly other proteins such as Rad9, Rad1, and Rad17/RFC complex (Abraham, 2001; Cortez et al., 2001). In addition, conditional deletion of ATR leads to G2 checkpoint defects and cell death (Cortez et al., 2001), indicating that ATR inhibition may be cytotoxic also to normal cells. However, short-term conditional expression of dominant negative ATR in human fibroblasts at a level that interfered with cell cycle checkpoint was not lethal (Cliby et al., 1998), raising the possibility that partial ATR inhibition may suppress checkpoints without causing cytotoxicity.

### 3.5 MMR deficiencies

The MMR pathway involves the removal of DNA base mismatches that arise during DNA replication or are caused by DNA damage. Mutations in seven known human MMR genes (*hMSH2, hMSH3, hMSH6, hMLH1, hMLH3, hPMS1,* and *hPMS2*) have been discovered, which lead to an inability to repair mismatches, causing an increased mutation rate and thus incidence of cancer. MMR deficiencies can be clearly observed in microsatellites - short tandem repetitive DNA sequences that are found throughout the genome (Laghi et al., 2008; Martin et al., 2010) and are predominantly linked to hereditary non-polyposis colorectal cancer (HNPCC), ovarian cancer, and leukemia (DeWeese et al., 1998; Pal et al., 2008; Whiteside et al., 2002). Cells mutated in either *hMSH2* or *hMLH1* have shown stronger mutator phenotypes and high microsatellite instability (MSI), which is often used as a marker for MMR deficiency (Jiricny & Nystrom-Lahti, 2000). A number of studies have also suggested a relationship between MMR deficiency and platinum-drug resistance (Aebi et al., 1996; Brown et al., 1997; Drummond et al., 1997; Lage & Dietel, 1999; Strathdee et al., 1999). However, the recent discovery that the MMR system plays an important role also in signaling the presence of DNA damage to the apoptotic machinery indicates that the function of MMR gene mutations may go beyond the mutator phenotype and MSI (D'Atri et al., 1998; Duckett et al., 1999; Hickman & Samson, 1999; Wu et al., 1999). Thus, MMR deficiency is likely to emerge as a frequent complication in the treatment of many types of cancers (Fleisher et al., 1999).

## 4. Targeting DNA repair pathways for cancer therapy

Radiation and genotoxic chemotherapies remain a mainstay of conventional cancer treatment and are likely to remain so for a foreseeable future. DNA damage responses are orchestrated by multiple signal transduction processes. Impaired DNA repair enables tumor cells to survive. Thus much current interest is focused on understanding how normal and tumor cells respond to DNA damage and determining whether DNA damage responses could be exploited or manipulated for therapeutic purposes.

DNA repair is a double-edged sword. First, deficiencies in DNA repair systems can lead to a higher incidence of cancer development; second, evidence also suggests that suppression of DNA repair capacity enhances the efficacy of conventional genotoxic anti-cancer agents, which has become an attractive strategy in anti-cancer therapeutics. Although promising, a full understanding of the biology and functions of the DNA repair pathways will be crucial for the future success of such approaches.

### 4.1 DNA damage checkpoint pathways

DNA damage checkpoints in the cell cycle serve as important barriers against cancer progression in human cells. Inhibition or inactivation of DNA damage checkpoint pathways can induce growth arrest, apoptosis and cellular senescence, and thus has been an attractive approach for cancer therapeutic interventions. The popular target proteins involved in these pathways are p53, ATM/ATR, and CHK1/CHK2. Efforts in targeting these proteins for therapeutic purposes are still in their infancy, and as understanding of the biological and molecular functions of these pathways becomes clearer, more effective and rational therapeutic strategies will likely emerge.

#### 4.1.1 p53

Cancers have mutated *p53*. One approach to target *p53* pathway is to re-introduce wild-type *p53* via gene replacement. The desired outcome is a suppression of tumor growth and sensitization of the cancer cells against cytotoxic DNA damaging agents (Blagosklonny & El-Deiry, 1996; Meng & El-Deiry, 1998). Several adenovirus-based application of wild-type *p53* have moved into human clinical trials in combination with cisplatin or carboplatin, and the data from these clinical trials suggest that this gene-therapy approach may provide an effective strategy for selective killing of epithelial cancer cells (Seth et al., 1996). Another approach to target *p53* is the selective depletion of the mutant p53 protein. Geldanamycin (GA), a benzoquinone ansamycin, depletes mutant p53 in breast, prostate, and leukemia cell lines (An et al., 1997) and prevents nuclear translocation of mutant p53 (Dasgupta & Momand, 1997). 17AA-geldanamycin, a GA analog, has undergone a phase I clinical trial (Nowakowski et al., 2006). Additionally, efforts in restoring normal function of mutant *p53* using other approaches have been tested (Hietanen et al., 2000; Selivanova et al., 1999). A synthetic 22-mer peptide derived from the C-terminal domain of p53 has been shown to have the ability to restore the normal function of p53 in *p53*-mutant cell lines, leading to suppressed cell growth (Selivanova et al., 1999). Actinomycin D and leptomycin B also showed their activities in reactivating wt *p53* in cervical carcinoma cells (Hietanen et al., 2000). However, a potential problem with most of these approaches is to protect normal cells that harbor functioning p53. Often, intervention of one pathway can lead to the secondary inactivation of downstream components which may generate even more aggressive cancers as shown by Martins and co-workers (Martins et al., 2006).

### 4.1.2 ATM/ATR

The clinical use of ATM inhibitors is based on the rationale that ATM signaling is dysfunctional in tumor cells and inhibition of its activity would sensitize tumor cells to agents that cause DSBs. Two very specific ATM inhibitors, KU55933 and CP466722, have been shown to be able to effectively inhibit ATM function, reducing the phosphorylation of a wide range of ATM substrates such as p53, NBS1, H2AX, and SMC1 (Hickson et al., 2004) and rapidly sensitizing cancer cells to ionizing radiation (Rainey et al., 2008; White et al., 2008). The specificity and efficacy of both ATM inhibitors implies the potential of using these inhibitors as radiosensitizers in future cancer clinical trials.

The ATR kinase plays a role of monitoring the effect the damage has on DNA replication or transcription rather than sensing the damage directly (Derheimer et al., 2007; Jiang & Sancar, 2006). In this regard, inhibition of ATR could be cytotoxic to both tumor and normal cells, and the toxicity caused by inhibition of ATR to normal cells can be too severe to be used in clinical setting. Unlike ATM, there are no specific ATR inhibitors available. Considering that ATR may compensate partly for loss of ATM function, selective inhibition of ATR could preferentially sensitize ATM-deficient tumors (Zhou et al., 2003).

### 4.1.3 CHK1/CHK2

Both CHK1 and CHK2 are important members of protein kinases involved in DNA damage checkpoint control. Loss of CHK1 and/or CHK2 functions in combination with genotoxic therapeutic agents would allow the generation of lethal DNA lesions that could lead to apoptosis and cell death. CHK1 responds primarily to replication folk abnormalities through ATR-dependent phosphorylation, which activates an array of downstream events to elicit cell cycle arrest, preserve replication fork viability, activate DNA repair mechanisms, and terminate the activated checkpoint to resume cell division cycle. Numerous studies have revealed that CHK1 is overexpressed in various tumor cells and down-regulation of CHK1 leads to spontaneous cell death (Collis et al., 2007; Feng et al., 2008; Jurvansuu et al., 2007; Leung-Pineda et al., 2009; Zhang et al., 2005; Zhang et al., 2009; Zhao & Piwnica-Worms, 2001). Thus, a strategy targeting the degradation of CHK1 in cancer cells would have a significant therapeutic implication in anti-cancer therapy.

CHK2 plays a similar role in DNA damage checkpoint pathways. Unlike CHK1, CHK2 is phosphorylated by ATM and is critical for DNA damage-induced apoptosis (Hirao et al., 2002; Takai et al., 2002). It regulates apoptosis in both ATM-dependent and ATM-independent manner (Hirao et al., 2002). Like p53, CHK2 is also a tumor suppressor and is highly expressed in both proliferating and differentiated normal tissues. Evidence has suggested that CHK2-p53 pathway is a determinant of the toxic side effects of anti-cancer treatment and CHK2 inhibitors may be very valuable for protecting tissues that are sensitive to DNA damage in patients with tumors that have a defective p53 pathway (Zhou et al., 2003). The therapeutic window of DNA-damaging therapies may be widened by CHK2 inhibitors via selective desensitization of normal cells.

To date, a number of CHK1 and CHK2 inhibitors have been developed (Collins & Garrett, 2005; Lin et al., 2006; Sorensen et al., 2003; Syljuasen et al., 2004; Wang et al., 2005). These compounds include G06976, isogranulutamide, SB-218078, urea, indolinones, XL844, and CEP-6367 (Collins & Garrett, 2005; Garber, 2005; Lin et al., 2006; Sorensen et al., 2003; Wang et al., 2005). However, the only known small-molecule inhibitor of CHK1 or CHK2 to enter clinical trial is XL844, which inhibits both CHK1 and CHK2 (Garber, 2005). While new checkpoint inhibitors are being developed, further understanding the functions of these

different tumor suppressors and checkpoint kinases in responding to DNA damage will better guide the use of selective checkpoint inhibitors in clinic.

### 4.2 Cell survival and proliferation pathways

Cell proliferation is governed by the cell cycle machinery which tightly controls cell cycle progression. Many kinases are involved in cell cycle regulation, including cyclin-dependent kinases (CDKs), PI-3 kinase, AKT, FOXO, EGFR, VGFR, and mTOR. The deregulation of many kinases is usually directly linked to cancer development. In solid tumors, changes in protein kinase expression levels and alterations in post-translational modifications can contribute to cancer and cancer progression. Thus, these kinases are often the targets for cancer therapeutic developments. In fact, protein kinase inhibitors are a major class of anti-cancer drugs.

#### 4.2.1 BCL-2 family proteins

The B-cell lymphoma 2 (BCL-2) family proteins have been studies extensively for the past decade because their importance in apoptosis, tumorigenesis, and cellular responses to anti-cancer therapy (Adams & Cory, 1998). The interplay among BCL-2 family members integrates intracellular signals to maintain a balance between newly forming cells and old dying cells. When anti-apoptotic BCL-2 family members such as BCL-2 and BCL-XL are over-expressed, apoptotic cell death is prevented. In mammalian system, it has become evident that both BCL-2 and BCL-XL are over-expressed in many types of cancer cells (Chao & Korsmeyer, 1998; Motoyama et al., 1995; Veis et al., 1993). They inhibit apoptosis by interacting with Bax or Bak. Targeting the anti-apoptotic BCL-2 family of proteins has thus become a popular approach to improve apoptosis and overcome drug resistance to cancer chemotherapy (Del Poeta et al., 2003; Minn et al., 1995; Yoshino et al., 2006). The dysfunction of apoptosis can lead to disastrous consequences such as cancer cell proliferation. The initiator and effector caspases are the key players in apoptotic cascade (Motoyama et al., 1995; Veis et al., 1993). There are two major apoptotic pathways converge on the effector caspases: the intrinsic cell-death pathway (also known as the mitochondrial pathway) and the extrinsic cell-death pathway. The intrinsic pathway is activated by a wide range of signals including radiation, cytotoxic drugs, cellular stress, and growth factor withdrawal. The activation of Caspase-9 by mitochondria is a central checkpoint of apoptosis, which triggers a cascade of caspase activation (caspase-3, -6, and -7), resulting in the biochemical changes associated with apoptosis. In contrast, the extrinsic cell-death pathway functions independently of mitochondria and is activated by cell surface death receptors such as Fas and tumor necrosis factor related apoptosis inducing ligand (TRAIL) receptors (Wajant, 2002). To date, 25 members of the BCL-2 family of proteins have been identified and they all can be defined by the presence of conserved motifs known as BCL-2 homology domains (BH1 to BH4). Both BCL-2 and BCL-XL contain all four BH domains while other members may only contain BH1 and BH2. Heterodimerization of these domains is essential for the pro-apoptotic activity. Thus, disruption of the protein-protein interaction among these BCL-2 family members has been a focus of the development of BCL-2 inhibitors (Cao et al., 2001), even though some anti-sense drug has also been developed (*e.g.*, Oblimersen sodium) (Rai et al., 2008). At present, many agents have been designed to target the bcl-2 family members at the mRNA or protein level. Agents with high specificity may provide excellent opportunities for cancer treatment but unexpected systemic toxicities may also be a problem

if only one member of the bcl-2 family proteins is targeted (Kang & Reynolds, 2009). One approach to enhance therapeutic efficacy and reduce severe side effects is to inhibit multiple bcl-2 members using a combination of drugs.

### 4.2.2 EGFR

The epithelial growth factor receptor (EGFR) is a tyrosine kinase that participates in the regulation of cellular homeostasis. Following ligand binding, EGFR stimulates downstream signaling cascades such as the JAK/STAT pathway, the PI-3K/AKT pathway, the RAS/MAPK pathway, and the PKC pathway, influencing cell proliferation, apoptosis, migration, survival, and complex processes including angiogenesis and tumorigenesis (Nyati et al., 2006). EGFR is overexpressed in tumor cells, causing resistance to radiation and chemotherapeutic agents (Chakravarti et al., 2004; Liang et al., 2003; Milas et al., 2004). Thus, targeting EGFR for cancer treatment has been intensely pursued and a series of EGFR-targeting drugs has been developed and approved by FDA for clinical use, most noticeably Gefitinib, Panitumumab, Erlotinib, and Cetuximab (Ljunhman, 2009). Increased EGFR expression has been linked to poor clinical outcome in patients with breast, oropharyngeal HNSCC, and ovarian cancers (Lo et al., 2005; Psyrri et al., 2005; Xia et al., 2009). Nuclear EGFR functions as a tyrosine kinase to phosphorylate and stabilize PCNA, and thus enhancing the proliferative potential of cancer cells (Wang et al., 2006). With its link to many different types of cancer, systematic laboratory and clinical research have facilitated the translation of EGFR inhibitors into common use in clinical oncology. For each new EGFR drug development, a complex series of preclinical and clinical tests have helped better understanding of the EGFR biology and advanced EGFR drug development in the both the laboratory and clinical settings.

### 4.2.3 CDKs

The Cyclin-dependent kinases (CDKs) are a family of serine/threonine kinases that regulate progression through each stage of the cell division cycle. In many cancers, CDKs are overactive or CDK-inhibiting proteins are not functional (Barriere et al., 2007; Malumbres & Barbacid, 2009). Thus, CDKs have been a major class of targets for deregulation in cancer cells to prevent unregulated proliferation of cancer cells. Two major cell cycle checkpoints are induced in response to DNA damage and take place before and after DNA synthesis during G1 and G2 phases. CHK1 and CHK2 are the two key transducers of these signaling pathways and they act indirectly on CDKs through their ability to inhibit members of the Cdc25 family of dual specificity phosphatases that dephosphorylate and activate CDKs (Bartek & Lukas, 2003). Roughly a dozen of CDK inhibitors have been developed to date (Collins & Garrett, 2005). Some are targeting multiple CDKs and others are targeting specific CDKs. However, the validity of these drug candidates should be carefully assessed because selectivity has been an issue. In addition, CDKs as effective anti-cancer targets may need to be re-evaluated, because genetic studies revealed that knockout of one specific type of CDK often does not affect proliferation of cells or has an effect only in specific tissue types (Malumbres & Barbacid, 2009). Furthermore, specific CDKs are only active in certain periods during the cell cycle. Therefore, the pharmacokinetics and dosing schedule of the candidate compound must be carefully evaluated to maintain active concentration of the drug throughout the entire cell cycle for cancer therapeutic purpose in clinical setting (Malumbres et al., 2008).

#### 4.2.4 AMPK

AMP-activated protein kinase (AMPK) is an enzyme that plays a role in cellular energy homeostasis. AMPK is a metabolic master switch regulating several intracellular systems including the cellular uptake of glucose, the β-oxidation of fatty acids and the biogenesis of glucose transporter 4 (GLUT4) and mitochondria (Bergeron et al., 1999; Durante et al., 2002; Ojuka, 2004; Thomson et al., 2007; Winder, 2001). Since its discovery, investigations into the regulation and the effects of AMPK have progressed very rapidly. Studies on the regulation of cellular proliferation by AMPK are becoming one of the critical areas in cancer research. Recent discoveries that three tumor-suppressors LKB1, p53, and TSC2 present either upstream (LKB1) or downstream (p53 and TSC2) have provided novel evidence that AMPK may function as a suppressor of cell proliferation. Thus inhibition of AMPK activity could lead to a suppressed cell proliferation. However, further studies are required for a full understanding of AMPK activation before it will emerge as an important target for the prevention and treatment of cancer.

#### 4.2.5 PI-3K/AKT/mTOR

The PI-3K/AKT/mTOR pathway is frequently dysregulated in cancers (Cortot et al., 2006; LoPiccolo et al., 2008; Morgensztern & McLeod, 2005; Yap et al., 2008). PI-3 kinase activates AKT which subsequently activates mTOR. In many cancers, this pathway is overactive, reducing apoptosis and allowing proliferation. The phosphatase PTEN, which is often mutated or underexpressed in many cancer cells, negatively regulates this pathway via inhibiting PI-3K (Carnero et al., 2008). Importantly, hyperactivation of the PI-3K/AKT/mTOR pathway was found to be associated with resistance to radiation and chemotherapy (Jameel et al., 2004). Therefore it presents a promising therapeutic target for tumor sensitization. There has been a tremendous interest in developing novel drugs against this pathway. Many small-molecule inhibitors against PI-3K, AKT, and mTOR have been developed and tested in tumor cells (Carnero et al.,2008; Fasolo & Sessa, 2008; Franke, 2008; LoPiccolo et al., 2008; Marone et al., 2008; Nakamura et al., 2005; Steelman et al., 2008; Tokunaga et al., 2008; Yap et al., 2008). One unique feature of targeting this pathway is to target the apoptosis-protecting role of AKT without negating its HR-suppressing function (Plo et al., 2008). Such compounds could lead to a strong sensitization of cancer cells to treatments requiring HR such as IR, cisplatin, MMC, and PARP inhibitors.

#### 4.2.6 VEGF

Vascular endothelial growth factor (VEGF) is a signal protein produced by cells to stimulate vasculogenesis and angiogenesis. VEGF is a major regulator of blood vessel formation and function. It controls several processes in endothelial cells such as proliferation, survival, and migration. However, it is still unknown how these processes are coordinately regulated to result in more complex morphogenetic events such as tubular sprouting, fusion, and network formation. Over-expression of VEGF has been observed across a wide range of tumor types including colon, lung, breast, renal, glioblastoma, ovarian, and prostate cancers (Ferrara, 2004; Hicklin & Ellis, 2005; Margolin, 2002). Without blood vessels, the tumors cannot grow. For this reason, tumor angiogenesis has become a critical target for cancer therapy. Most common anti-VEGF strategies include ligand-binding with antibodies to prevent VEGF from binding to VEGF receptors (VEGFR1 and VEGFR2). Angiogenesis inhibitors targeting VEGF have shown antitumoral activity in preclinical and clinical trials. Currently available agents with established role include the anti-VEGF humanized mAb

bevacizumab, which is approved for the treatment of metastatic HER2/NEU-negative breast cancer (Miller et al., 2007). In many recent clinical trials, angiogenesis inhibitors were also being used in combination with conventional chemotherapy (Thanigaimani et al., 2010). One advantage of using angiogenesis inhibitors for cancer treatment is its low toxicity and less susceptibility to the induction of acquired drug resistance. However, like many other anti-cancer drugs, these inhibitors will need to be tested vigorously in the future clinical trials before they can be approved for use of cancer therapy alone because therapy with these inhibitors often does not prolong survival of cancer patients for more than months (Quesada et al., 2010).

#### 4.2.7 HSP90

Heat shock protein 90 (HSP90) is a molecular chaperone involved in protein folding, cell signaling, and tumor repression. It is one of the most abundant proteins expressed in cells (Csermely et al., 1998). HSPs are a class of proteins that protect cells when stressed by elevated temperatures, dehydrating, or by other means. In this sense, HSPs seem to serve as biochemical buffers for the numerous genetic lesions that are characteristic of most human cancers. HSP90 is known to play a Janus-like role in the cell where it is essential for the creation, maintenance, and destruction of proteins. Its normal function is critical to maintaining the health of cells, whereas its dysregulation may lead to carcinogenesis. Cancerous cells over express a number of biologically critical proteins, including growth factor receptors, such as EGFR, or signal transduction proteins such as PI-3K and AKT (Lurje & Lenz, 2009). HSP90 stabilizes these proteins (Sawai et al., 2008), and loss of HSP90-mediated stabilization of these proteins selectively affects cancer cells (Mohsin et al., 2005; Stebbins et al., 1997). Another important role of HSP90 in cancer is the stabilization of mutant proteins such as v-Src, the fusion oncogene *Bcr/Abl*, and mutant forms of *p53* that appear during cell transformation (Calderwood et al., 2006). HSP90 is also required for induction of VEGF and nitric oxide synthase (NOS) (Fontana et al., 2002). Both are important for de novo angiogenesis that is required for tumor growth beyond the limit of diffusion distance of oxygen in tissues (Calderwood et al., 2006). HSP90 also promotes the invasion step of metastasis by assisting the matrix metalloproteinase MMP2 (Eustace et al., 2004). Together with its co-chaperones, HSP90 modulates tumor cell apoptosis mediated through effects on AKT (Sato et al., 2000), tumor necrosis factor receptors (TNFR) and nuclear factor-κB (NF-κB) function (Whitesell & Lindquist, 2005). Finally HSP90 participates in many key processes in oncogenesis such as self-sufficiency in growth signals, stabilization of mutant proteins, angiogenesis, and metastasis. Thus, as expected, the use of HSP90 inhibitors in cancer treatment has demonstrated its importance as a therapeutic target and shown promising effects in clinical trials. For example, the HSP90 inhibitor, geldanamycin has been used as an anti-tumor agent (Goetz et al., 2003). The drug was originally thought to function as a kinase inhibitor but was subsequently shown to be an HSP90 inhibitor where it uses a compact conformation to insert itself into the ATP binding site.

### 4.3 Accessory factor

Targeting DNA repair accessory factors as a therapeutic strategy has shown great promise for cancer treatment. The question remains as to whether these factors can be readily targeted, because many of them are multi-functional proteins involved in multiple pathways. For example, poly(ADP-ribose) polymerase (PARP) has recently emerged as one of the 'hot' anti-cancer targets. Inhibition of PARP impairs a tumor cell's DNA repair

activity, disabling its defense against DNA-damaging chemotherapy (Kling, 2009; Bryant & Helleday, 2004). Another DNA repair accessory factor, HMG-1, which is a specific marker of necrotic cell death, has also been suggested to facilitate protein-DNA and protein-protein interactions, enhancing effective binding of receptors such as progesterone receptor (PR) to its target DNA sequences and thus promoting cell survival (Onate et al., 1994). If inhibition of these factors can lead to cancer cell killing, it may provide clinically feasible opportunities for improved anti-cancer therapies. However, all the anti-cancer therapies targeting DNA repair pathways may also affect normal cells.

### 4.3.1 BRCA1/BRCA2

As stated earlier in this chapter, individuals with heterozygous, deleterious, germ line mutations in either *BRCA1* or *BRCA2* genes exhibit high life-time risks of developing breast, ovarian, and other types of cancer. A significant development in exploiting the DNA repair defect in *BRCA* mutant cells has been the use of synthetic lethality approaches. Cells lacking functional BRCA1 or BRCA2 have a deficiency in the repair of DSBs by HR. This deficiency results in the repair of these lesions by NHEJ or single-strand annealing (SSA) instead (Turner et al., 2005). Although it is still an area of intensive investigation, haplo-insufficiency phenotype remains a possibility for *BRCA1* and *BRCA2* mutant carriers (Santarosa & Ashworth, 2004). Agents that cause an increase in DSBs which are normally repaired by HR should selectively only affect BRCA-deficient cells, not normal cells (Tutt et al., 2006). This provides an ideal target for therapeutic intervention. Based on the concept that a lethal synthetic interaction between two genes occurs when mutation of either alone is compatible with viability, but mutation of both leads to cell death (Hartwell, 1997; Kaelin, 2005), a DNA repair protein, poly(ADP-ribose) polymerase (PARP), was identified as a synthetic lethal partner of BRCA1 and BRCA2 (Bryant et al., 2005; Farmer et al., 2005). Inhibition of this protein leads to severe and highly selective toxicity in BRCA-deficient cells. Similar results were obtained on xenografts and in animal models of spontaneous BRCA2 loss of function (Bryant et al., 2005; Farmer et al., 2005; Hay et al., 2005). PARP inhibitors have been previously used as chemosensitizing and radiosensitizing agents. However, the use of these agents as therapeutic in the treatment of BRCA-deficient tumors is novel. There is still a great deal of research and development needed to be done before these PARP inhibitors can serve as medicine.

### 4.3.2 BRCA-FA

BRCA-FA pathway is essential for DNA damage response in cells. Loss of a functional BRCA-FA DNA damage response pathway, breast and ovarian tumors as well as leukemia can develop. BRCA-FA derived tumor cells must rely on alternative pathways for survival. Thus, to develop an effective therapeutic strategy, understanding specifically how these alternative pathways compensate for defects in the BRCA-FA pathway to promote survival is essential. The emerging role of BRCA-FA proteins in HR implies that tumor cells derived from mutations in these genes should have impaired HR. Several lines of evidence have supported this possibility, because *BRCA1, BRCA2, BRIP1/FANCJ*, and *PALB2/FANCN*-deficient cells all demonstrate defects in HR, consistent with a role for the BRCA-FA pathway in HR (Litman et al., 2005; Niedernhofer et al., 2005; Scully & Livingston, 2000, Venkitaraman, 2002; Xia et al., 2006). Thus there are opportunities to target the DNA repair defect in BRCA-FA tumors by increasing lesions repaired by HR. It was recently illustrated

that inhibiting BER increased the number of DSBs and also enhanced RAD51 foci formation, suggesting an increased activity in HR (Helleday et al., 2005). Based on this observation, it is reasonable to hypothesize that cells defective in HR would be sensitive to inhibition of BER. In fact, treatment of BRCA-FA-deficient cells with an inhibitor of the BER enzyme, PARP, leads to a dramatic reduction in cell survival, while BRCA-FA proficient cells were only mildly impacted by the PARP-inhibition (Helleday et al., 2005). Another important feature of targeting the BRCA-FA pathway is that cells defective in BRCA-FA are likely to repair DSBs by compensatory pathways such as NHEJ or SSA. For example, it was demonstrated that disruption of the NHEJ pathway cooperated with inactivation of the BRCA-FA pathway to enhance radiosensitivity in mouse embryonic fibroblasts (MEFs) (Houghtaling et al., 2005). Thus, by inactivating the BRCA-FA pathway, it may be possible to sensitize cancer cells that have become resistant to DNA cross-linking agents. The drug resistance and BRCA-FA pathway was also linked by a study in which cisplatin sensitive ovarian cancer cells developed cisplatin resistance by restoring expression of a previously silenced *FANCF* gene (Taniguchi et al., 2003). Similarly, restoring *BRCA2* gene expression in tumor cells leads to an acquired drug resistance to mytomycin C (MMC) (Chen et al., 2005). Thus, targeting BRCA-FA pathway may be effective in treating resistant tumors. However, directly targeting BRCA-FA pathway may be too toxic for most cells. It is conceivable that constituitive activation of the BRCA-FA pathway will be useful to dysregulate the pathway for therapeutic gain. In particular, deubiquitination of FANCD2 by USP1 could be targeted to reduce, but not to disable, the BRCA-FA pathway function. Clinically, it will be most beneficial if inhibitors of BRCA-FA pathway are used in combination with radiation and/or DNA cross-linkers.

#### 4.3.3 Ribonucleotide reductase (RNR)

The ribonucleotide reductase (RNR, also known as ribonucleoside diphosphate reductase) is a ubiquitous radical-containing enzyme that catalyzes the formation of deoxyribonucleotides from ribonucleotides, which are used in the synthesis of DNA (Elledge et al., 1992). The reaction catalyzed by RNR is strictly conserved in all living organisms (Torrents et al., 2002). Furthermore RNR plays a critical role in regulating the total rate of DNA synthesis so that DNA to cell mass is maintained at a constant ratio during cell division and DNA repair (Herrick & Sclavi, 2007). An unusual feature of the RNR enzyme is that it catalyzes a reaction that proceeds via a free radical mechanism of action (Eklund et al., 1997; Stubbe & Riggs-Gelasco, 1998). The levels and activity of RNR are highly regulated by the cell cycle and DNA checkpoints which maintain optimal dNTP pools required for genetic fidelity. The enzyme can be regulated by two factors: by transcription of the genes or by allosteric control of RNR by triphosphate effectors. When DNA damage occurs, a transcriptional induction of a new protein called p53R2, which is a p53-inducible RNR, is observed (Guittet et al., 2001; Shao et al., 2004). p53R2 has been shown to play an important role in supplying deoxyribonucleotides for DNA repair synthesis (Guittet et al., 2001; Tanaka et al., 2000; Yamaguchi et al., 2001) and the expression of p53R2 has been found to be up-regulated in various types of cancers (Devlin et al., 2008). Because inhibition of RNR has severe impact on DNA replication and repair, it makes an attractive target for cancer therapies. In fact, inhibition of p53R2 resulted in sensitization to both radiation and chemotherapeutic agents by attenuation of cell cycle checkpoints and enhanced apoptosis (Delvlin et al., 2008; Wang et al., 2009; Yokomakura et al., 2007).

### 4.3.4 Thymidylate synthase

Thymidylate synthase (TS) is another important DNA repair accessory factor essential for DNA replication and repair. TS generates thymidine monophosphate (dTMP) which is subsequently phosphorylated to thymidine triphosphate (dTTP) for use in DNA synthesis and repair. TS is often found overexpressed in tumors and it has been suggested that TS overexpression promotes cell proliferation and resistance to radiation (Saga et al., 2002; Voeller et al., 2004). This makes TS an attractive cancer therapeutic target. Many TS inhibitors, such as fluorinated pyrimidine fluorouracil or certain folate analogues, have been developed and used in clinic for decades to treat advanced cancers (Clamp et al., 2008; Longley et al., 2003; Rustum, 2004; Showalter et al., 2008).

### 4.3.5 Proteasome

Proteasomes are very large protein complexes and act as a 'vacuum-cleaner' to degrade unneeded or damaged proteins by proteolysis. The proteasomal degradation pathway is essential for many cellular processes, including the cell cycle, the regulation of gene expression, and responses to genotoxic stresses (Lodish et al., 2004). In response to cellular stresses such as infection, heat shock, or oxidative damage, heat shock proteins that identify misfolded or unfolded proteins and target them for proteasomal degradation are expressed. Both HSP27 and HSP90 have been implicated in increasing the activity of the ubiquitin-proteasome system, though they are not direct participants in the process (Garrido et al., 2006). HSP70, on the other hand, binds exposed hydrophobic patches on the surface of misfolded proteins and recruits E3 ubiquitin ligases such as CHIP to tag the proteins for proteasomal degradation (Park et al., 2007). Similar mechanisms exist to promote the degradation of oxidatively damaged proteins via the proteasome system. In particular, proteasomes localized to the nucleus are regulated by PARP and actively degrade inappropriately oxidized histones (Bader & Grune, 2006). Oxidized proteins, which often form large amorphous aggregates in the cell, can be degraded directly by the 20S core particle without the 19S regulatory cap and do not require ATP hydrolysis or tagging with ubiquitin (Shringarpure et al., 2003). However, high levels of oxidative damage increases the degree of cross-linking between protein fragments, rendering the aggregates resistant to proteolysis. Dysregulation of the ubiquitin proteasome system may contribute to several neural diseases. It may lead to brain tumors such as astrocytomas (Lehman, 2009). Proteasome inhibitors have effective anti-tumor activity in cell culture, inducing apoptosis by disrupting the regulated degradation of pro-growth cell cycle proteins (Adams et al., 1999). This approach of selectively inducing apoptosis in tumor cells has proven effective in animal models and human trials. Bortezomib, a molecule developed by Millennium Pharmaceuticals and marketed as Velcade, is the first proteasome inhibitor to reach clinical use as a chemotherapy agent. Bortezomib is used in the treatment of multiple myeloma (Fisher et al., 2006). Notably, multiple myeloma has been observed to result in increased proteasome levels in blood serum that decrease to normal levels in response to successful chemotherapy (Jakob et al., 2007). Studies in animals have indicated that bortezomib may also have clinically significant effects in pancreatic cancer (Nawrocki et al., 2004; Shah et al., 2001). Preclinical and early clinical studies have been started to examine bortezomib's effectiveness in treating other B-cell-related cancers (Schenkein, 2002), particularly some types of non-Hodgkin's lymphoma (O'Connor et al., 2005). The molecule ritonavir, marketed as Norvir, was developed as a protease inhibitor and used to target HIV infection. However, it has been shown to inhibit proteasomes as well as free proteases; to be specific,

the chymotrypsin-like activity of the proteasome is inhibited by ritonavir, while the trypsin-like activity is somewhat enhanced (O'Connor et al., 2005). Studies in animal models suggest that ritonavir may have inhibitory effects on the growth of glioma cells (Laurent et al., 2004). Proteasome inhibitors have also shown promise in treating autoimmune diseases in animal models. For example, studies in mice bearing human skin grafts found a reduction in the size of lesions from psoriasis after treatment with a proteasome inhibitor (Zollner, *et al.*, 2002). Inhibitors also show positive effects in rodent models of asthma (Elliott et al., 1999). Labeling and inhibition of the proteasome is also of interest in laboratory settings for both *in vitro* and *in vivo* study of proteasomal activity in cells. The most commonly used laboratory inhibitors are lactacystin, a natural product synthesized by *Streptomyces* bacteria (Orlowski, 1999), and peptide MG132. Fluorescent inhibitors have also been developed to specifically label the active sites of the assembled proteasome (Verdoes et al., 2006).

#### 4.3.6 MicroRNAs

MicroRNAs (miRNAs) are evolutionarily conserved small non-coding RNAs of 18-25 nucleotides in length that regulate gene expression. Several miRNAs have been found to have links with some types of cancer (He et al., 2005; Mraz et al., 2009). MicroRNA-21 is one of the first microRNAs that was identified as an oncomiR. A study of mice altered to produce excess c-Myc — a protein with mutated forms implicated in several cancers — shows that miRNA has an effect on the development of cancer. Mice that were engineered to produce a surplus of types of miRNA found in lymphoma cells developed the disease within 50 days and died two weeks later. In contrast, mice without the surplus miRNA lived over 100 days (He et al., 2005). Leukemia can be caused by the insertion of a viral genome next to the 17-92 array of microRNAs leading to increased expression of this microRNA (Cui et al., 2007). Another study found that two types of miRNA inhibit the E2F1 protein, which regulates cell proliferation. miRNA appears to bind to messenger RNA before it can be translated to proteins that switch genes on and off (O'Donnell et al., 2005). By measuring activity among 217 genes encoding miRNA, patterns of gene activity that can distinguish types of cancers can be discerned. miRNA signatures may enable classification of cancer. This will allow doctors to determine the original tissue type which spawned a cancer and to be able to target a treatment course based on the original tissue type. miRNA profiling has already been able to determine whether patients with chronic lymphocytic leukemia had slow growing or aggressive forms of the cancer (Lu et al., 2005). Transgenic mice that over-express or lack specific miRNAs have provided insight into the role of small RNAs in various malignancies (Zanesi et al., 2010). A novel miRNA-profiling based screening assay for the detection of early-stage colorectal cancer has been developed and is currently in clinical trials. Early results showed that blood plasma samples collected from patients with early, resectable (Stage II) colorectal cancer could be distinguished from those of sex-and age-matched healthy volunteers. Sufficient selectivity and specificity could be achieved using small (less than 1 mL) samples of blood. The test has potential to be a cost-effective, non-invasive way to identify at-risk patients who should undergo colonoscopy (Nielsen et al., 2010).

## 5. Personalized medicine

Cancer is a multifaceted disease with many subtypes. Patients with identical clinical and pathological phenotypes often show different responses to the same therapy (Ely, 2009).

Today, numerous prescriptions written annually are ineffective in treating cancer patients (Phillips et al., 2001). This will increase the likelihood of overtreatment, the risk of adverse drug reactions (ADRs) in patients, and the costs of care for an individual patient (Ingelman-Sundberg, 2001). Thus, optimized treatments for individual patients will eventually lead to better clinical outcomes and patient satisfaction (Spears et al., 2001). Over the past decade, advances in genomics and proteomics have accelerated our understanding of individual differences in genetic makeup, allowing a more personalized approach to healthcare (Faratian et al., 2009; Marko-Varga et al., 2007; Phan et al., 2009; Yeatman et al., 2008). The prediction of treatment outcome based on an individual's biological information represents the future of oncology medicine – so called personalized medicine. Over the past ten years, personalized medicine has emerged as a rapidly advancing field in cancer patient care. Personalized medicine utilizes in-depth clinical, genomic, and proteomic information about an individual patient in order to determine which therapies will be safer and more effective for his/her care, matching the "right patients" to the "right drugs". This new paradigm will no doubt improve health outcomes and patient satisfaction. However, decision making based on personalized biological information is far from simple. Understanding the probabilities, risk reduction, and short- and long-term consequences associated with each possible treatment based off the testing results is difficult. It requires not only accurate data collection and storage but also highly trained medical professionals to dissect the information and to use the complex data to make wise and effective treatment decisions.

Even though many challenges are still ahead of us as clinical data continues to be generated and published. This new concept of personalized medicine will affect everyone in the cancer treatment community. How quickly the new integration of personal information into more effective health-care delivery occurs will largely depend on the development of predictive tools and the education of health-care providers. In addition to scientific and technological advances, personalized medicine also holds the promise of great cost-saving measures in health-care reform.

## 6. Future outlooks

As the DNA repair field continues to evolve, a better understanding of the DNA repair mechanisms and the players involved will certainly affect the development of anti-cancer therapies. Insights from understanding and targeting DNA damage response pathways have launched a new era in cancer therapy. As it appears, the weakness of tumor cells is that they either lack the ability to repair DNA damages or rely on other compensating DNA repair mechanisms for cell survival. Thus, new therapeutic development should focus on attacking these compensating pathways to compromise tumor cell viability, and this approach promises highly targeted therapies that potentially bypass the need for traditional radiation or chemical cancer therapies.

## 7. Conclusions

A rapid pace of discovery and development of anti-cancer therapy driven by new technologies makes cancer research into an exciting phase. Many previous studies have shed light on the complexity of tumor biology, showing that tumors rarely have similar sets of mutations in common. The fact that many tumors have defects in DNA repair pathways and/or cell cycle checkpoints presents unique opportunities for anti-cancer therapeutic

exploitation. With a better understanding of the mechanisms involved in DNA repair and DNA damage responses, tumor-specific therapies may be developed.

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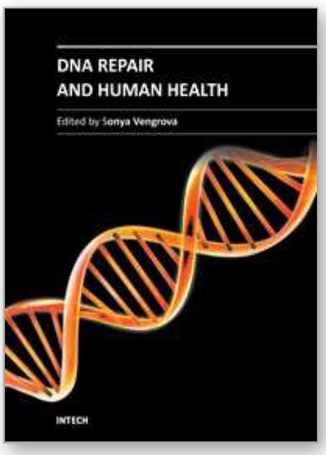


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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair 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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