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The Association of the DNA Repair Genes with Acute Myeloid Leukemia: The Susceptibility and the Outcome After Therapy

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1. Introduction

Acute myeloid leukemia (AML), the most common acute leukemia in adults, is a clonal hemopoietic disorder that is frequently associated with genetic instability characterized by a diversity of chromosomal and molecular abnormalities. There are a lot of reports that show that human cancer can be initiated by DNA damage caused by ultraviolet (UV), ionizing radiation, and environmental chemical agents. Many genes encode proteins that function to protect cells against genetic instability through numerous mechanisms, including deoxyribonucleic acid (DNA) repair pathways and protection against oxidative stress.

DNA repair pathways play an important role in maintaining the integrity of the genome, and it is obvious that defects in repair pathways are involved in many different types of diseases, including leukemia and cancer (Seedhouse, 2002).

DNA damage repair and cell-cycle checkpoints are the most important defense mechanisms against mutagenic exposures. The most important DNA-repair pathways in human cells are: direct repair, base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), Double Strand Break Repair (DSB repair) and translesion DNA synthesis (TLS). Each pathway repairs a different type of lesion (D'Andrea, 2010). The NER pathway mainly removes bulky distortions in the shape of the DNA double helix. The BER pathway is responsible for removal of oxidized DNA bases that may arise endogenously or from exogenous agents. The DSB pathway is responsible for repairing double-strand breaks caused by a variety of exposures, including ionizing radiation. There are two distinct and complementary pathways for DSB repair-namely, homologous recombination (HR) and nonhomologous end joining (NHEJ).

Recent studies have suggested that DNA damage was related to the pathogenesis of some diseases such as AML. Therefore, some DNA repair genes may be involved in AML susceptibility (Allan, 2004; Kuptsova, 2007; Seedhouse, 2002, 2004; Voso, 2007).

Exposure to carcinogenic and genotoxic compounds causes DNA damage, and the cells have developed multiple DNA repair pathways to protect themselves from different types of DNA damage.

Polymorphisms in DNA repair genes, including those involved in base excision repair (BER), nucleotide excision repair, mismatch repair and double strand break repair have been implicated in carcinogenesis. Common polymorphisms in DNA repair genes may alter protein function and an individual's capacity to repair damaged DNA. Deficits in repair capacity may lead to genetic instability and tumorigenesis.

Studies have noted associations between risk of de novo AML and DNA repair gene polymorphisms (Matullo et al., 2006; Seedhouse et al., 2004). Increased risk of therapy-related AML was also linked to several gene polymorphisms in base excision repair (BER; XRCC1 Arg399Gln), nucleotide excision repair (NER; XPD Lys751Gln), and DSB repair (RAD51 G135C and XRCC3 Thr241Met) pathways (Allan et al. 2004; Seedhouse et al., 2002, 2004) and may be linked to secondary AML etiology through failure to recognize or excise accumulated DNA lesions.

2. Mechanism of DNA repair

DNA damage response pathways, some of the genes known to participate in each of these pathways, their modes of action are summarized in Table 1. These categories are not exclusive; there may be functional overlap between repair systems. For example, certain types of base damage can be repaired by base excision repair, nucleotide excision repair or homologous recombinational repair.

DNA repair genes may also have great implications in the therapeutic outcome of certain cancer treatments. Most antileukemic drugs interact with target cell DNA and exert their cytotoxic effects preferentially in replicating cells. In addition to the primary DNA lesions, secondary DNA alterations induced in the course of repair processes also contribute to the cytotoxic effects of DNA-reactive agents (Rajewsky & Müller, 2005).

Although there are several reports on associations between polymorphisms in DNA repair genes and cancer risk (Goode et al., 2002), fewer studies have been conducted to evaluate relationships between DNA repair gene polymorphisms and response to treatment.

2.1 Direct repair mechanism

This is the simplest repair mechanism compared to other repair system regarding number of molecules involved. It is an enzyme-catalyzed process used to correct the most frequent cause of point mutations in humans.

In direct repair mechanisms, the lesion is removed or reversed by a single step reaction restoring the local sequence to its original state. There are several direct repair enzymes, each having a different substrate. For example, O⁶-methyl guanine DNA methyltransferase (O⁶-MT, the product of the MGMT gene) repairs the alkylation damage. MGMT is important in the repair of alkylation damage. The alkyl group from the lesion is transferred to a cysteine residue in the active site of MGMT (Hazra et al., 1997). In 20% of human tumor cell lines the MGMT activity is decreased and the sensitivity to alkylating agent is increased (Sancar, 1995), but there are few data which suggest that mutations in the MGMT gene contribute to cancer (Wang L et al, 1997; Yu Z et al, 1999).

The functional status of the O⁶-MT pathway may be important in patients treated with alkylating agents, for O⁶-methylation of guanine appears to be an important effect of some members of that class of drugs (Kaina & Christmann, 2002). High levels of O⁶-MT are often found in AML blasts, which are thereby rendered resistant to certain alkylators (Gerson & Trey, 1988).

Pathway	Function	Genes Involved	References
Direct Repair Mechanism	Reverses damage to restore DNA integrity.	DNA photolyase, O ⁶ -MGMT	Kaina et al., 2007; Mitra, 2007
Base Excision Repair (BER)	Repair of damaged bases or single-strand DNA breaks	OGG1, XRCC1, APE1, PARP,	Chaudhry, 2007; Yu et al., 1999; Hazra et al., 2007
Nucleotide Excision Repair (NER)	Excision of a variety of helix-distorting DNA lesions	XPA, XPB, XPC, XPD, XPE, XPF, XPG, RAD23, TFIIH, RPA1, RPA2, RPA3, PCNA	Kang et al., 2011; Reardon & Sancar, 2005; Yu et al., 1999
Mismatch Repair (MMR)	Repair of mispaired nucleotides	MSH2, MSH6, MSH4, PMS1, MLH1, PMS2, MLH3, PMS2L3, PCNA, RPA	Jiricny, 2006; Martin et al., 2010; Papouli et al., 2004; Surtees et al., 2004
Homologous recombination (HR)	Repair of double strand DNA break	RAD51, RAD51B, RAD51C, RAD51D, XRCC2, XRCC3, RAD52, RAD54, BRCA1, BRCA2, RAD50, NBS1, MRE11	Li & Heyer, 2008; Sung & Klein, 2006;
Nonhomologous End Joining (NHEJ)	Repair of double strand DNA breaks	XRCC4, XRCC5, XRCC6, XRCC7, LIG4, XLF,	Burma et al., 2006; Shrivastav et al., 2008
Translesion Synthesis (TLS)	Bypass of DNA adducts during DNA replication	POLK, POLI, POLZ, REV7, REV1, POLH,	Lehmann, 2006

Table 1. DNA Damage Response Pathways

2.2 Base Excision Repair

Base excision repair (BER) is the predominant DNA damage repair pathway for the processing of small base lesions, derived from ionizing radiation (Chen et al., 2010), oxidation, hydrolysis, or deamination and alkylation damages. The repair system involves three steps: removal of damaged bases from DNA by DNA glycosylases, then formed abasic site is removed and finally gap is filled by DNA polymerase.

In BER, the removal of a single modified base from one DNA strand is performed by DNA glycosylases, specialized enzymes. Some of these glycosylases show pronounced lesion specificity, others recognize multiple, and structurally different damaged bases. The apurinic/aprimidinic (AP) site left behind after cleavage of the N-glycosylic bond is hydrolyzed by an AP endonuclease, and the 5'-deoxyribose phosphate is excised by a phosphodiesterase. The resulting single-nucleotide gap is then filled by polymerase β and ligated. Alternatives to this common BER pathway include the excision of a short

oligonucleotide patch containing the AP site and filling of the gap by polymerase δ or ϵ . Base alterations caused by a large variety of agents and processes (e.g. spontaneous deamination, ionizing radiation, alkylating agents, DNA replication errors) are processed by BER. A common feature of the DNA lesions recognized by BER glycosylases is that they do not significantly distort the DNA helix (Yu, 2009).

Common single-nucleotide polymorphisms (SNPs) in the 8-oxoguanine glycosylase 1 (OGG1), X-ray repair cross-complementing group1 (XRCC1), and the apyrimidinic endonuclease-endonuclease 1 (APE1) genes in the BER pathway have been studied for their influences in induction of DNA damage (Chen et al., 2010).

XRCC1

X-ray repair cross-complementing group 1 (XRCC1) is required for repairing single-strand breaks and damaged bases in DNA. The XRCC1 protein interacts with DNA polymerase β , DNA ligase III and polyadenosine diphosphate-ribose polymerases (PARP) involved in excision and recombinational repair pathways (Cardecott, 2003). The XRCC1 has no known enzymatic activity (Thompson et al., 1990) and participates as a scaffold protein in both single-strand break repair and base excision repair activities. The human XRCC1 gene is located on chromosome 19q13.2 which contains 17 exons and encodes a protein of consisting 633 amino acids (Lindahl & Wood, 1999). More than 60 validated single-nucleotide XRCC1 polymorphisms are known. The most studied single nucleotide polymorphisms are Arg194Trp on exon 6, Arg280His on exon 9, and Arg399Gln on exon 10. All these polymorphisms were studied with association to different types of cancer.

The presences of the variant (399Gln and 194Trp) alleles have been shown to be associated with measurable reduced DNA repair capacity and increased risk of several types of cancers (Dufloth et al., 2005; Goode et al., 2002; Hu et al., 2005; Hung et al., 2005). In our study involving 43 patients with acute leukemia and 40 controls, for XRCC1 Arg194Trp and Arg399Gln polymorphism, we observed the relationship of XRCC1 polymorphisms with acute myeloid leukemia (our own unpublished data). Our cases with a codon 194 Trp/Trp homozygous variant as well as the heterozygous Arg/Trp variant had an increased risk of AML with a greater risk in the case of the homozygous codon 194 Trp/Trp allele (OR=2.28, 95% for Trp/Trp). There was a significantly high risk of AML among patients who were carriers of the variant allele 399Gln (OR=2.45, 95% for Gln/Gln and OR=1.90, 95% for Arg/Gln).

A study by Seedhouse et al. (2002) reported that the presence of at least one XRCC1 399Gln allele indicated a protective effect for the allele in controls compared with patients with AML, particularly therapy-related AML (t-AML) (odds ratio OR=0.44; 95% confidence interval CI=0.20~0.93). According to the same study patients who develop AML as a result of therapy for a primary malignancy are more likely to have the wild-type XRCC1 399 arginine allele. El-Din et al. (2010) reported that XRCC1 gene polymorphism is important in the pathogenesis of de novo AML. El-Din et al. (2010) observed that AML patients expressing XRCC1 Arg194Trp polymorphism are at high risk of developing AML; in addition, a significant risk in the development of AML was observed when XRCC1 Arg399Gln polymorphism was present. In a study of 372 patients with acute myeloid leukemia, Kuptsova et al. (2007) reported no significant associations between XRCC1 polymorphisms and treatment outcomes.

hOGG1

The human 8-oxoguanine DNA glycosylase 1 (hOGG1) encoded by the hOGG1 gene can remove 8-hydroxy-2-deoxyguanine (8-OHdG) from damaged DNA as a part of the base excision repair pathway (Kohno et al., 1998). The hOGG1 gene is located on chromosome 3p26.2 (Kohno et al., 1998). Although, several polymorphisms in the hOGG1 gene have been described, the most commonly studied polymorphism is an amino acid change from serine to cysteine at codon 326 (Ser326Cys). Several studies have reported that Ser326Cys polymorphism in OGG1 gene may increase susceptibility to for bladder (Arizono et al., 2008), lung (Park et al., 2004), oesophageal (Xing et al., 2001), gallbladder and gastric (Tsukino et al., 2004) cancer development.

Liddiard et al (2010) provided a study about the importance of 8-oxoguanine in AML including the genotyping of 174 AML patients for the hOGG1 Ser326Cys polymorphism. Using Affymetrix microarrays they showed that the prevalence rate of hOGG1 expression was 33% and correlated strongly with adverse cytogenetics. hOGG1-expressing patients had a worse relapse-free survival and overall survival and an increased risk of relapse at 5-years of follow-up. According to Liddiard et al. (2010) hOGG1 is an important prognostic marker that could be used to sub-stratify AML patients to predict those likely to fail conventional chemotherapies and those likely to benefit from novel therapeutic approaches that modulate DNA repair activity. In a recent study Stanczyk et al. (2011) have demonstrated that Cys/Cys variant of the OGG1 Ser326Cys polymorphism may increase the risk of ALL (OR=5.36, P<0.001).

APE1

The human apurinic/apyrimidinic endonuclease (APE1) plays a central role in the base excision repair pathway, which is the primary mechanism for the repair of DNA damage caused by oxidation and alkylation. The APE1 gene is located on chromosome 14q11.2-q12 and contains five exons. A total of 18 polymorphisms in APE1 have been reported, but the most extensively studied polymorphism is Asp148Glu (Gu et al., 2009). The damaged bases of purine and pyrimidine are recognized and excised by specific DNA glycosylases, leaving abasic sites. Apurinic/apyrimidinic endonuclease then incise the DNA 5' to the abasic sites; further repair proceeds to short-patch (when the gap is only one nucleotide) or long-patch (when the gap is two or more nucleotides) subpathways of base excision repair (Lo et al., 2009). In a hospital-based matched case-control study with 730 lung cancer cases and 730 cancer-free controls Lo et al. (2009) found that the -656T>G variant in the APE1 promoter was associated with a significantly decreased risk for lung cancer. In a study of 320 pediatric patients with acute leukemia, Krajcinovic et al. (2002) reported no significant associations between polymorphic APE1 148Glu and XRCC1 194Trp variants and event-free survival. Ji et al. (2020) performed a meta-analysis to explore the association between the APE1 Asn148Glu gene polymorphisms and lung cancer risk. They suggested that the APE1 T1349G (Asp148Glu) polymorphism was not associated with lung cancer risk among Asians or Caucasians. But, the APE1 G allele was an increased risk factor for developing lung cancer among smokers. Pre-clinical and clinical data indicate a role for APE1 in the pathogenesis of cancer and in resistance to DNA-interactive drugs, particularly monofunctional alkylators and antimetabolites (Wilson & Simeonov, 2010).

2.3 Nucleotide Excision Repair

Nucleotide excision repair is the most studied DNA repair system in humans (de Laat et al., 1999). The NER pathway is responsible for repair of bulky distortions in the shape of the DNA double helix such as chemical adducts, pyrimidine dimers, and cross-links caused by endogenous and environmental lesions (Riedl et al., 2003; van der Wees et al., 2007; Wood, 1989). This pathway may also be important in conferring resistance to chemotherapeutic agents such as platinum-based chemotherapy (Kennedy & D'Andrea, 2006).

NER has five stages: recognition of the bulky damage which distorts the DNA helix; hydrolyzing a phosphodiester bond in the deoxyribose backbone on the 5' side of the lesion; excising the damage; filling in the resultant gap using the information from the complementary strand; closing the nicked DNA to generate intact strand (Yasbin, 2002).

NER can be divided into two subpathways (Transcription coupled NER and Global genomic NER) that differ only in their recognition of helix-distorting DNA damage (Hanawalt, 2002). Global genome repair is a slow process of inspecting the entire genome for damage (Kennedy & D'Andrea AD, 2006). Transcription-coupled repair is more rapid, highly specific and efficient and repairs DNA damage that blocks the progression of RNA polymerase II.

The actual repair mechanism appears to be identical in transcription-coupled and in global-genome repair. However, the damage recognition in global-genome repair does not involve the RNA polymerase, but is performed by the XPC and HHR23 proteins. Following lesion recognition, however, both repair systems use TFIIH components such as XPB and XPD, as well as the single-strand binding protein RPA and the XPA protein to fully unwind and mark the lesion. The damaged segment of DNA is excised through 5'-incision by the XPF endonuclease and 3'-incision by the XPG endonuclease. The DNA gap is filled by DNA polymerases δ or ϵ supported by PCNA and sealed by a DNA ligase, presumably DNA ligase I (Kennedy & D'Andrea, 2006; Yu et al., 1999).

XPD

The XPD gene (xeroderma pigmentosum group D, also known as ERCC2) encodes a DNA helicase involved in nucleotide excision repair pathway. The XPD gene maps to chromosome 19q13.3 and consists of 23 exons (Wang et al., 2008). Its protein is 761 amino acids in length. The XPD protein repairs a wide range of structurally unrelated lesions, such as bulky adducts and thymidine dimers (Braithwaite et al., 1999). The DNA repair process and gene transcription are coupled via activity of the TFIIH complex, a protein complex with functions including transcription, NER, transcription-coupled repair, apoptosis, and cell cycle regulation. XPD protein is involved in maintaining the stability of the TFIIH complex. The XPD gene product has an ATP-dependent DNA helicase activity (Laine et al, 2007).

Because of the biological significance of XPD, the XPD Lys751Gln (2251A>C) polymorphism has been a common subject of studies in different malignant diseases in the last years. Although the XPD 751Gln variant was associated with an increased risk of esophageal cancer and acute lymphoid leukemia (Wang et al., 2008) Allan et al. (2004) investigated XPD Lys751Gln polymorphism in 341 adult British AML patients and observed that the XPD codon 751 polymorphism is an independent prognostic marker for disease-free survival and overall survival in elderly AML patients treated with chemotherapy, and specifically that the glutamine variant was associated with a poorer prognosis relative to the lysine variant. In a pediatric study, Mehta et al. (2006) found no influence of XPD751 genotype on susceptibility to de novo AML in children. In another study, Kuptsova-Clarkson et al. (2010)

evaluated the role of XPD and XRCC1 gene polymorphic variation in response to induction chemotherapy, toxicities and survival in a population of 293 predominantly Caucasian adult patients treated for AML. Kuptsova-Clarkson et al. (2010) had reported that in AML, variation in the XPD gene may be associated with suboptimal DNA repair activity and may thus predispose to therapy-related AML development. In a UK study by Seedhouse et al. (2002), therapy-related AML was not associated with XPD genotypes.

There have been studies of XPD, involved in NER, and survival of patients with AML (Allan et al., 2004). In a study of elderly patients with AML conducted by researchers in the United Kingdom, modestly increased hazard ratio (HR) of 1.30 and 1.19 were found for disease-free and overall survival, respectively, by XPD variant genotypes. However, in a study of pediatric patients with acute myeloid leukemia conducted by the Children's Oncology Group (Mehta et al., 2006) survival and treatment-related mortality were not associated with XPD codon 751 genotypes.

2.4 Mismatch repair

DNA mismatch repair (MMR) plays a critical role in maintaining genomic integrity. MMR is responsible for correction of mismatched basepairs which occurs through processes including misincorporations during DNA replication, formation of heteroduplexes, and secondary structure such as imperfect palindromes (Bishop et al., 1985).

In addition, MMR can also process some types of DNA damage. MMR deficient tumors display widespread alterations in simple repetitive DNA sequences, a phenomenon also called microsatellite instability; MSI (Li, 2008). The repair mechanism is similar to that of excision repair; a patch of nucleotides is removed from one strand, and followed by resynthesis and ligation processes.

There are two types of mismatch repair, long-patch and short-patch which have been found in human cells. In short-patch repair system there are three enzymes possessing nicking activities specific for mismatch repair; T/G specific (Wiebauer & Jiricny, 1989), A/G specific, and all type mismatch nicking enzymes (Yeh et al., 1991). That enzymes have different mode of action, but in either an A/G mismatch or a T/G mismatch, it is usually the guanine that remains untouched by mismatch specific glycosylases (Wiebauer & Jiricny, 1989).

Long patch can repair all types of mismatches. Long-patch MMR removes a patch of one of the DNA strands from an incision on the to-be-removed strand to 90~170 nucleotides beyond the mismatch (Fang & Modrich, 1993; Yu et al., 1999).

Defects in the MMR pathway significantly increase the mutation frequency and promote oncogenesis. It has been documented that defects in MMR genes, are the genetic basis for certain types of hereditary and sporadic cancers, including hereditary nonpolyposis colorectal cancer (Mao et al., 2008). There are some studies looking at the incidence of MMR deficiency (microsatellite instability; MSI) in AML (Mao et al., 2008). Genomic instability in AML has led to a search for MSI in AML patients, but the results are quite controversial. While several studies have reported MSI in AML (Das-Gupta et al., 2001; Sheikhha et al., 2002), a study of 132 cases failed to confirm the previous results (Rimsza et al., 2000). According to Rimsza et al. (2000) MMR deficiency was associated with all stages of AML, but the rate of the deficiency was much higher in patients with refractory and relapsed AML than in de novo AML patients, suggesting that the loss of MMR function could contribute to the refractory and relapsed disease.

2.5 Double Strand Break repair

Double strand break repair (DSB) is responsible for the repair of double strand DNA breaks. DNA double strand breaks represent the most important class of DNA damage because, if unrepaired, they can result in a loss of genetic material, chromosome abnormalities and possibly cell death. Moreover, the breaks are prone to nuclease attack with subsequent destruction (Rufer & Morgan, 1992). Double strand breaks (DSBs) can be produced by exogenous agents such as ionizing radiation, some chemotherapeutic drugs, endogenous formed reactive oxygen species. When DNA replication forks encounter DNA single strand breaks or other types of lesion, it might result in formation of DSBs. In addition, DSBs are generated to initiate recombination between homologous chromosomes during meiosis, and also during the immunoglobulin class-switch recombination. Repair of DSBs is more difficult than other type of DNA damage because there is no undamaged template available (Khanna & Jackson, 2001).

Direct DSBs are mainly repaired by non-homologous end joining (Sargent et al., 1997), whereas replication-associated DSBs are repaired by homologous recombination (HR) and related replication repair pathways (Iliakis et al., 2004).

2.5.1 Non-homologous End Joining

Non homologous end joining (NHEJ) is active in all phases of the cell cycle and is considered to be the most important DSB repair pathway in mammalian cells. The NHEJ pathway is simpler than HR and requires no complementary template. The protein components of NHEJ include the catalytic subunit of DNA protein kinase (DNA-PKcs), the two regulatory subunits of the DNA-PK complex Ku70 and Ku80, DNA ligase IV with its cofactor XRCC4 (the X-ray cross complementing group 4 protein) and the nuclease artemis (Drouet et al., 2005; Khanna & Jackson, 2001). The Ku70/Ku80 (Ku) heterodimer is the first protein to bind to the damaged DNA ends. When bound to the DSB, Ku recruits and activates DNA-PKcs. These proteins play an important role in DNA DSB repair and will act as tumor suppressors. However, either the DNA protein kinase complex, or its three subunits individually, can also act as oncogenes, depending on the compartment of the cell in which they are expressed and on the cell cycle phase (Gullo et al., 2006).

XRCC4

The X-ray cross-complementing group 4 (XRCC4) gene is one of the specific members of the NHEJ system. Some of the SNPs of XRCC4 have been found to be associated with the susceptibility to different types of cancer. Two single nucleotide polymorphisms (SNPs) of XRCC4, one splicing-site polymorphism (SNP14 rs1805377:A4G) and one intronic polymorphism (SNP1 rs2075685:G4T), have been studied, and the results are conflicting (Allen-Brady et al., 2006; Fu et al., 2003). The protein encoded by XRCC4 consists of 336 amino acid residues distributed among 8 exons, and has a long helical stem domain responsible for multimerization and interaction with DNA ligase IV (Junop et al., 2000). By forming a complex with DNA ligase IV and DNA-dependent protein kinase, XRCC4 functions in the repair of DNA double-strand breaks by non-homologous end joining (NHEJ) and the completion of V(D)J recombination events (Hayden et al., 2007). The NHEJ pathway is required not only for normal development but also for suppression of tumors. Since it is one of the ubiquitous NHEJ components, XRCC4 might be considered as a potential tumor suppressor gene in cancer and leukemia.

There have been several studies showing that variations of the XRCC4 gene are associated with prostate (Chang et al., 2008), gastric (Chiu et al., 2008), and breast cancer (Fu et al., 2003). Therefore, XRCC4 and the DNA double-strand break repair pathway may serve as a common mechanism of early carcinogenesis. In a recent study, Wu et al. (2008) investigated the association between XRCC4 gene polymorphisms and oral cancer. Their findings suggest that the presence of the A allele of XRCC4 codon 247 was associated with a higher susceptibility to oral cancer, and the A allele of XRCC4 codon 247 may be a useful novel marker in oral oncology for primary prevention and intervention.

XRCC5, XRCC6, XRCC7

A key component of the NHEJ pathway is the DNA-dependent Protein Kinase (DNA-PK), which consists of a heterodimeric DNA targeting subunit (i.e., Ku70/Ku80, encoded by XRCC6/XRCC5 genes) and a catalytic subunit DNA-PKcs, encoded by XRCC7 gene (Smith & Jackson, 1999).

XRCC5 (X-ray repair cross-complementing 5) is a gene involved in repair of DNA double-strand breaks. Abnormal expression of the XRCC5 protein is associated with genomic instability and an increased incidence of cancers. The XRCC5 gene mapped to chromosome 2q35, encodes the 80-kDa subunit of the Ku heterodimer protein, the DNA-binding component of the DNA-dependent protein kinase. The Ku80 is essential for maintaining genomic integrity through its ability to bind DNA double-strand breaks and to facilitate repair by the nonhomologous end-joining pathway in mammalian cells (Taccioli et al., 1994).

XRCC6 (X-ray repair complementing defective repair in Chinese hamster cells 6) is a helicase involved in DNA repair and chromatin remodeling. The XRCC6 gene (also called Ku70) maps to chromosome 22q13.2-q1. Ku70 plays an important role in the DNA double-strand breaks repair and maintenance of genomic integrity. Genetic variations within human Ku70 have been demonstrated to be associated with increased risk of several types of cancers (Wenshan et al., 2011).

XRCC7 (X-ray repair cross complementing group 7) is located on chromosome 8q12, span about 110-180 kb and contains 100 exons. The human XRCC7 gene encodes DNA-PKcs, which is recruited to the site of DSBs by the Ku70/Ku80 heterodimer to form an active DNA-PK complex (Siple et al., 1995). The expression of Ku70 and XRCC7 is elevated in bladder tumor tissue and head and neck cancer cell lines, respectively (Stronati et al., 2001; Sturgis et al., 1999) and Ku70 may function as a caretaker gene for the development of T-cell lymphomas (Li et al., 1998). XRCC7 encodes DNA-PKcs, which also may have a caretaker role in colon carcinogenesis. Therefore, the variants of the Ku70 and XRCC7 genes could be expected to have an effect on DSB repair, and thus, on carcinogenesis. The Ku70 polymorphism is associated with risk of breast cancer (Fu et al., 2003), and the XRCC7 polymorphism is associated with risk of glioma (Wang et al., 2004). According to Wang et al. (2008) the XRCC7 polymorphism appears to be involved in the etiology of human bladder cancer. This data support the notion that the XRCC7 polymorphism is implicated in cancer risk.

Given the crucial roles of the NHEJ pathway in DNA repair (Gullo et al., 2006), it is possible that the XRCC5, XRCC6 and XRCC7 variants may modulate the risk of cancer, including leukemia. It has been shown that increased NHEJ activity is due to the presence of XRCC5 and XRCC6 protein, which results in genomic instability in myeloid leukemia cells (Gaymes et al., 2002). XRCC5 and XRCC6 may function as a caretaker gene for the development of T-cell lymphomas, while XRCC7 may have a caretaker role in colon carcinogenesis (Wang et

al., 2009). In a recent study, Wang et al. (2009) have investigated the association between the X-ray repair cross complementing group XRCC5, XRCC6 and XRCC7 polymorphisms and risk of AML in Chinese population. In this case-control study in a southern Chinese population three polymorphisms, XRCC5 2R/1R/0R, XRCC6 -61C>G and XRCC7 6721G>T were investigated. For the XRCC7 6721G>T polymorphism among AML cases and controls no significant association was observed ($P=0.68$). Significant association was observed ($P=0.04$) for the XRCC6 -61C > G polymorphism. Their analysis revealed that compared with the XRCC6 -61CC wild type homozygote, the -61CG heterozygotes had a significant 43% decreased risk of AML (adjusted OR=0.57; 95% CI=0.35~0.92) and subjects carrying -61CG/GG variant genotypes had 45% decrease in risk of AML (adjusted OR=0.55; 95% CI=0.34~0.89). For the XRCC5 2R/1R/0R polymorphism, Wang et al. (2009) found that XRCC5 1R/0R genotype was associated with a 2.60-fold increase in risk of AML (95% CI=1.42~5.92) compared with the 2R/2R genotype. They found a significant association with the polymorphisms of XRCC5 2R/1R/0R, XRCC6 -61C>G and the risk of AML, but there was no evidence for an association between the XRCC7 6721G>T variants and AML.

2.5.2 Homologous recombination

Homologous recombination (HR) is one of the main pathways for the repair of DNA double strand breaks (DSBs). HR is thought to be particularly important in DNA repair occurring during cellular replication (Rollinson et al., 2007). Although HR is indispensable for maintaining genome integrity, it must be tightly regulated to avoid harmful outcomes. The repair process is complex and involves many proteins working coordinately. Key players include MRE11, RAD50, NBS1 (MRN), RAD51, RAD51B, RAD51C, RAD51D, XRCC2, XRCC3, RAD52, RAD54 and BRCA2 (Lieberman, 2008). A number of polymorphic genes involved in this pathway have been studied in AML.

Homologous recombination mechanism starts with degradation of the DNA next to the double-strand break, leaving single-strand ends. Next the single-strand end of the damaged strand invades and binds to its complementary DNA sequence on the homologous duplex. This is associated with the displacement of the cross-complementary strand toward the gap site, where it serves as a template for gap-filling DNA synthesis. The repair sequence is terminated by religation of the repair patches. This mechanism requires the presence of undamaged homologous DNA, and increased activity of this repair pathway has been observed.

RAD51 protein catalyzes homologous recombination through its homologous pairing and strand exchange activities. RAD52 may modulate these activities through its RAD51-interacting region. The ability of RAD52 to induce homologous recombination requires its binding to the p34 subunit of RPA. This RPA binding domain is at amino acids 221–280. Recall that RPA is also involved in NER—this may provide a linkage between these two repair systems (Yu Z et al., 1999).

XRCC3

The X-ray repair cross-complementing group 3 (XRCC3), codes for a protein participating in homologous recombination repair of DNA double-strand breaks. XRCC3 is a member of the RAD-51-related protein family. RAD-51-like proteins are known to participate in homologous recombination to maintain chromosome stability and repair DNA damage (Brenneman et al., 2000). XRCC3-deficient cells demonstrated genetic instability and

increased sensitivity to DNA damaging agents (Griffin, 2002). The human XRCC3 gene is located on chromosome 14q32.3 and consists of 17870 bases. The protein product of XRCC3 gene contains 346 amino acids. According to NCBI SNP database, XRCC3 gene has 111 SNPs. The main polymorphism in this gene involves the change of threonine (Thr) to methionine (Met) at codon 241 in exon 7 (Shen et al., 1998). Little is known about the functional consequences of this variation, although some studies observed a positive relation between the Thr241Met polymorphism and an increased risk for skin (Winsey et al., 2000), bladder (Matullo et al., 2001), breast (Garcia-Closas et al., 2006) and lung (Jacobsen et al., 2004) cancers.

A meta-analysis of 48 case-control studies, including 24975 cancer patients and 34209 controls, investigated the associations of the three DNA repair gene XRCC3 polymorphisms (Thr241Met; 4541A4G; 17893A4G) with cancer risk (Han et al., 2006). According to this meta-analysis individuals carrying the XRCC3 Met/Met genotype have a smaller cancer risk compared with the individuals with the Thr/Thr or Thr/Met genotype (OR=1.07; P=0.008; 95% CI=1.02~1.13) (Han et al., 2006). For A4541G, a significantly increased risk was associated with the variant genotypes (G/G+A/G), compared with the wild homozygote A/A genotype (OR=1.09; P=0.004; 95% CI, 1.03~1.15). For A17893G, individuals with the variant genotypes (G/G+A/G) had a significantly decreased cancer risk, compared with individuals with the A/A genotype under a dominant genetic model (OR=0.92; P=0.0004; 95% CI=0.87~0.96). Han et al. (2006) consider that the XRCC3 could not be a major increased risk factor for cancer but it might represent a low-penetrance susceptible gene especially for cancer of breast, bladder, head and neck, and non-melanoma skin cancer

In their study Seedhouse et al. (2004) have observed that the presence of variant XRCC3 241Met was associated with an increase in the risk of developing therapy-related AML of more than 8 fold, whereas the increase in risk for the development of de novo AML was nearly 4 fold.

RAD 51

The RAD51 gene plays an important role in homologous recombination and in maintaining the genetic stability of the cell. In HR, RAD51 interacts with and is stabilized by XRCC3, during strand invasion and cross-strand resolution. RAD51 is a central protein in the HR repair pathway binding to DNA and promoting ATP-dependent homologous pairing and strand transfer reactions.

The RAD51 gene is located on chromosome 15q15.1 and consists of 36998 bases. The protein product of RAD51 has 6 domains, one for DNA binding, one for ATPase activity, and the other domains are specific to action of RAD51. According to NCBI SNP database, RAD51 gene has 296 SNPs. The most important polymorphism identified for RAD51 is G135C SNP in 5' untranslated region. The RAD51 G135C polymorphism is associated with RAD51 protein over-expression (Richardson et al., 2004). Regarding the role of RAD51 in the homologous DNA repair mechanism, several studies have examined the relationship between RAD51 G135C polymorphism and risk of certain cancers. However the results from these studies are conflicting. Further studies are needed to establish the role of RAD51 G135C polymorphism in human carcinogenesis.

Voso et al. (2007) found an increased frequency of the RAD51 135C allele in AML, mainly in de novo AML, when compared with controls, but not between therapy-related AML (t-AML) and controls. Other reports found increased frequency of the RAD51 135C allele in

t-AML patients compared with controls (Seedhouse et al., 2004), suggesting an effect of RAD51 over-expression during leukemogenesis induced by chemotherapy or radiotherapy. According to Bhatla et al. (2008) RAD51 gene polymorphism did not influence the outcome of AML therapy in the study of de novo AML patients. On the contrary, Liu et al. (2008) concluded that RAD51 gene polymorphism was significantly related to response to therapy, adverse effects, and prognosis of AML and reported that detection of the RAD51 gene polymorphism genotypes may be useful in selecting individual chemotherapy regimens for patients with AML. Also, Bolufer et al. (2007) reported that the RAD51 gene polymorphism showed significant unfavorable outcome among AML patients. In their study, Bathla et al. (2008) observed a doubling of risk of AML in children with a RAD51 G135C variant allele and a wild-type XRCC3 Thre241Met genotype. In addition risk of AML was significantly increased in children with at least one variant XRCC3 Thr241Met allele. In antithesis, risk was not significantly elevated in children with variant alleles at both wild-type XRCC3 Thre241Met and RAD51 G135C. Liu et al. (2008) found that XRCC3 gene polymorphism was significantly related to response to therapy and prognosis of AML and reported that detection of the XRCC3 gene polymorphism genotypes may be useful in selecting individual chemotherapy regimens for AML patients.

2.6 Translesion synthesis

Translesion synthesis is an important mechanism by which cells replicate past DNA damage. The sliding clamp DNA polymerase processivity factors play a central role in this process. The clamps are dimeric in bacteria and trimeric in eukaryotes and archaea, raising the question of whether more than one polymerase can interact with the clamp simultaneously (Lehmann, 2006).

3. Inherited human disease with leukemia susceptibility

Several studies have demonstrated that the genes involved in DNA repair and maintenance of genome integrity are critically in protecting against mutations that lead to cancer and/or inherited human disease (Table 2).

Syndrome	Gene(s) involved	Chromosome	References
Fanconi anaemia (FA)	FANC-A to FANC-N	16q24.3	Levitus et al., 2004; Steensma, 2007;
Ataxia-telangiectasia (AT)	Ataxia-telangiectasia (AT)	11q22.3	Savitsky et al., 1995; Thompson & Schild, 2002
Nijmegen breakage syndrome (NBS)	NBS1 (Nibrin)	8p21	Digweed et al., 1999; Varon et al. 2003
Bloom syndrome (BLM)	BLM (RECQL3)	15q26.1	Ellis & German, 1996; Thompson & Schild, 2002
Seckel Syndrome	ATR	3q22-24	Casper et al., 2002;

Table 2. DNA repair defective syndromes

Several of these diseases include an inherent predisposition to hematologic malignancies, including AML. The clinical features and molecular characteristics of several of the inherited disorders with leukemia risk are described below.

Fanconi anemia (FA) is a rare disorder with a birth incidence around 3 per million. FA is an autosomal recessive and rarely X-linked syndrome which is characterised by congenital abnormalities, defective haemopoiesis (bone marrow failure) and a high risk of developing AML and certain solid tumours.

Affected individuals can have mild growth retardation, hypo- or hyperpigmented areas of the skin, skeletal defects including radial limb defects (absent thumb with or without radial aplasia), abnormalities of ribs and hips and scoliosis, cardiac and renal malformations, genital abnormalities (especially undescended testes, testicular agenesis, hypospadias). Other associated anomalies include microphthalmia and developmental delay (Grompe & D'Andrea, 2001). The phenotypic abnormalities are variable and there is marked variability between affected individuals in the same family (Alter, 1993).

The Fanconi anemia defect results from biallelic mutation of any one of thirteen known Fanconi anemia genes (A, B, C, D1, D2, E, F, G, I, J, L, M, N). The proteins encoded by these Fanconi anemia genes cooperate in a common DNA repair pathway, referred to as the Fanconi anemia /BRCA pathway. In this pathway, eight of the Fanconi anemia proteins (A, B, C, E, F, G, L, M) are assembled into a core complex that functions as an E3 ubiquitin ligase. This ligase activates in response to DNA damage from a crosslinking drug, adding a 76-amino acid moiety onto two other Fanconi proteins, D2 and I. This monoubiquitinated D2/I complex is translocated into chromatin, where it interacts with the downstream Fanconi proteins BRCA2, N, and J. This combination of proteins mediates the DNA repair process. After the repair has occurred, there is another enzyme complex, called USP1, which removes the ubiquitin and inactivates the pathway. Knocking out any of the proteins in this pathway causes FA (D'Andrea, 2010).

FANCA, located on chromosome 16q24.3, is the most commonly mutated gene and is altered in 60-65% of FA patients (Steensma, 2007). FANCC and G mutations account for almost 25%, and FANCE and FANCF for a further 8%.

Approximately one third of patients homozygous for a Fanconi anemia gene mutation will develop a hematologic or solid tumors by the age of 40 years (Kennedy & D'Andrea, 2006). Fanconi anemia patients develop predominately myeloid malignancies (the most common hematologic malignancy is AML), although numerous other cancers arise, including squamous cell carcinomas of the head and neck or gynecologic system, skin cancers, esophageal cancers and liver tumors (Alter, 2003; Rosenberg et al, 2008).

Fanconi anemia patients have a systemic DNA repair defect that results in a low tolerance for DNA damaging chemotherapeutic agents.

Ataxia-telangiectasia (AT) is a rare autosomal recessive disorder. This human disease is characterized by cerebellar degeneration, immunodeficiency, hypogonadism, growth retardation, genome instability, extreme sensitivity to radiation and predisposition to cancer (Taylor & Byrd, 2005). The disease is caused by homozygous mutations in the gene encoding the ATM protein kinase that plays a critical role in DNA damage detection and regulates DNA double-strand break repair (Mavrou et al, 2008). The ATM gene is located on chromosome 11q23. When ATM is dysfunctional or absent, cells are able to progress from G1 to S phase and initiate DNA replication in the presence of DNA damage.

Approximately one third of AT patients develop cancer, mainly leukemias and lymphomas which develop in childhood and are a common cause of death (Ball & Xiao, 2005; Gumy-Pause et al, 2004). Solid tumors in AT patients are usually adenocarcinoma of the stomach, dysgerminoma, gonadoblastoma and medulloblastoma (Mavrou et al, 2008).

Bloom's syndrome (BS) is a rare autosomal recessive syndrome of growth retardation, telangiectasia manifest by facial erythema, immunodeficiency, and skull abnormalities. BS patients also are predisposed to cancer, as they develop mostly leukemias and lymphomas in about half of the patients. This disorder is most commonly found in the Ashkenazi Jewish population resulting from a founder mutation (Ellis et al, 1998). It is characterised by low birth weight, growth deficiency, characteristic facies (long thin face, prominent nose) sun-sensitivity, immunodeficiency and infertility in males.

Bloom's syndrome arise through mutations in both copies of the BLM gene, which is located on chromosome 15 at 15q26.1. This gene encodes a member of the RecQ family of DNA helicases (BLM) that is important in maintaining appropriate DNA conformation during chromosomal recombination and repair. Together with topoisomerase III, BLM resolves Holliday junctions during homologous recombination (HR) by a mechanism called double-junction dissolution that is distinct from classical Holliday junction resolution and that prevents erroneous exchange of flanking sequences (Steensma, 2007).

Nijmegen breakage syndrome (NBS) is an autosomal recessive disorder that is most commonly found in Eastern Europe. NBS is caused by abnormalities in the NBN gene at 8p21 (Varon et al, 2003), which encodes the protein NBN (NBS1). Complete loss of this polypeptide is lethal. The NBS gene encodes a 95-kDa protein that binds with MRE11 and RAD50 to form a nuclease-containing protein complex that appears to be involved in homologous and nonhomologous recombination. Clinical features include growth retardation, microcephaly, skin findings such as vitiligo and café au lait spots, skeletal defects, immunodeficiency and propensity to infection. Radiation hypersensitivity is a hallmark of the disease, along with a predisposition to cancer, most notably lymphomas (Digweed et al, 1999). The most common cause of death for NBS patients is neoplasia (Steensma, 2007). Although the predominant neoplasm is lymphoma, both lymphoid and myeloid leukemia have been reported (Resnick et al, 2002).

Seckel syndrome (SCKL) is a rare autosomal recessive disorder associated with short stature, prenatal and postnatal growth retardation, characteristic craniofacial dysmorphism (bird-headed face including prominent beaked nose, micrognathia and malformed ears), mental deficiency, microcephaly, and skeletal defects (Faivre et al, 2002). Hematological abnormalities, including pancytopenia, myelodysplasia and acute myeloid leukemia, have been reported in some patients with Seckel syndrome (Chanan-Khan et al, 2003; Hayani et al, 1994). A gene for Seckel syndrome was mapped on chromosome 3q22.1-q24. The ataxia-telangiectasia and RAD3-related (ATR) gene is mutated in Seckel syndrome, and encodes an phosphatidylinositol-3-kinase-like kinase which has distinct, but overlapping functions with ATM in co-ordinating the response to DNA damage. ATR is activated by single stranded DNA whilst ATM responds to DNA double strand breaks (Casper et al, 2002; Steensma, 2007).

4. Conclusion

Genetic variations in genes involved in DNA repair may influence both cancer susceptibility and treatment response. However, in AML, the relevance of these genetic variations remains

to be fully established. There is evidence that some polymorphisms in DNA repair genes play a role in carcinogenesis, notably hOGG1 Ser326Cys, XRCC1 Arg194Trp, XRCC3 Thr241Met, RAD51 G135C and XPD Lys751Gln. Additional studies of these and other DNA repair polymorphisms will provide essential information about the relationships between the DNA repair mechanisms and risk of AML.

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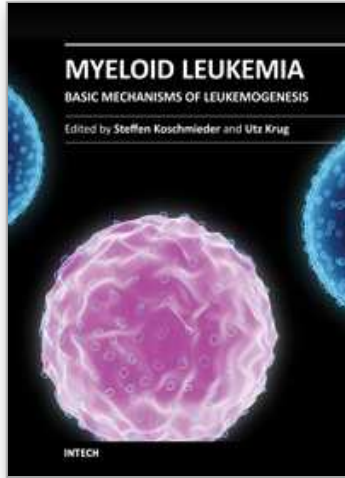
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