14

DNA Repair Deficiency Associated with Hematological Neoplasms

Panagiota Economopoulou, Vassiliki Pappa, Sotirios Papageorgiou, John Dervenoulas and Theofanis Economopoulos
Second Department of Internal Medicine, Propaedeutic, University of Athens, Medical School, University General Hospital "Attikon" Greece

1. Introduction

The genome of living organisms is constantly subjected to conditions that induce damage to DNA. A wide variety of DNA lesions are produced either as the result of normal metabolic processes or exogenous sources (ionizing radiation, UV light) (Seviour and Lin 2010). This damage to genomic material represents a persistent threat to genomic stability.

Mammalian cells have developed a range of molecular mechanisms capable of responding to DNA damage. These mechanisms include activation of DNA damage repair pathways or tolerance systems, initiation of complex regulatory networks that coordinate cell cycle progression and repair and induction of apoptosis if errors are detected (Madhusudan and Middleton 2005). At a cellular level, if a DNA lesion is misrepaired, it can lead to genomic instability. It is therefore essential for a cell to efficiently respond to DNA damage. Different DNA Repair Mechanisms exist and play a major role in restoring genomic integrity. These include: The Direct Repair Pathway (DR), Base Excision Repair Mechanism (BER), Nucleotide Excision Repair Pathway (NER), Non-Homologous End Joining (NHEJ), Homologous Recombination (HR) and DNA Mismatch Repair Pathway (MMR). It is quite obvious that any defect in these mechanisms can lead to improperly repaired DNA lesions and genomic abnormalities, which constitute the hallmark of tumorigenesis (Cline and Hanawalt 2003, Hwang et al. 1999). Indeed, mutations and polymorphisms of DNA repair genes have been correlated with different hereditary and sporadic cancer types (Altieri et al. 2008).

Hematological malignancies account for about 8% of all cancers in men and 6% of all cancers in women. There is a considerable body of evidence that suggests a strong association between DNA repair deficiency and hematological malignancies. This article is meant to serve as an overview of the relevant literature focusing on mutations and polymorphisms of DNA repair genes that predispose to certain hematological malignancies. We also discuss how defects in DNA repair affect sensitivity to chemotherapy.

2. DNA repair mechanisms

Below, we briefly summarize our current knowledge regarding DNA Repair Mechanisms.

2.1 Direct Repair (DR)

Direct Repair of DNA damage (DR) is the simplest repair process that copes with the repair of O^6-alkylguanine adducts in humans. O^6-alkylguanine transferase (AGT, also known as MGMT) is the key enzyme that reverses O^6-alkyl-guanine to guanine by transferring the inappropriate methyl group to one of its own cysteine residues, leading to inactivation of itself (Scharer 2003).

2.2 Nucleotide Excision Repair (NER)

The Nucleotide Excision Pathway (NER) processes bulky DNA lesions with potential to block DNA replication or transcription (de Laat et al. 1999, Gillet and Scharer 2006, Lockett et al. 2005, Park and Choi 2006, Sancar 1996, Wood 1997). It mainly corrects products of UV light and chemotherapy (reviewed in (Scharer 2003)). When NER mechanism repairs damaged lesions in non-transcribing genomic DNA, it is called Global Genome NER (GG-NER). In contrast, Transcription-Coupled NER (TC-NER) removes damaged DNA specifically on the RNA polII transcribed strand of transcriptionally active DNA.

2.3 Base Excision Repair (BER)

The Base Excision Repair (BER) is a pathway that removes damaged bases from DNA, but also repairs single-strand breaks. Several variations exist, including short-patch BER (SP-BER) that typically replaces a single nucleotide and long-patch BER (LP-BER) where repair synthesis can extend beyond one nucleotide. The two pathways progress through different processes that initially involve removal of the damaged base by glycolases (Fortini and Dogliotti 2007, Fortini et al. 1999).

2.4 Mismatch Repair (MMR)

The Mismatch Repair Pathway (MMR) recognizes and repairs base-base mismatches and insertion/deletion loops that could arise during DNA replication (Jiricny 2006). Therefore, it contributes to the accuracy of DNA replication process (Jiricny 1998).
Defects in MMR result in Microsatellite Instability (MSI), a form of genetic instability characterized by frequent errors occurring during the replication of short nucleotide repeats (Velangi et al. 2004).

2.5 Double Strand Break (DSB) Repair

DNA double strand breaks (DSBs) occur as the result of two simultaneous nicks in opposite strands of the DNA helix. Although they are formed much less frequently than other forms of DNA damage, the consequences of DSBs can be severe. They are induced by exogenous sources (ionizing radiation, UV light, topoisomerase inhibitors) or arise spontaneously during natural processes (DNA synthesis, V-(D)-(J) recombination) (Karagiannis and El-Osta 2004).
A cell has evolved the DNA damage response (DDR) to initially respond to a DSB. DDR involves the sensing of the damage, followed by transduction of the damage signal to either cell cycle checkpoints and DSB repair or apoptosis. DDR is dependent on transient recruitment of MRN (MRE11/RAD50/NBS1) complex followed by activation of two phosphatidylinositol-3-related kinases, ATM and ATR that phosphorylate a variety of molecules to execute DDR (Figure 1) (Bakkenist and Kastan 2004). The activation of cell cycle checkpoints aims at the growth arrest of damaged cells and allows DSB repair to mend the damage. A DSB can be repaired by two separate mechanisms, either Homologous Recombination (HR) or Non Homologous End Joining (NHEJ) (Kim et al. 2006).

2.6 Homologous Recombination (HR)

Homologous Recombination (HR) is a highly complex pathway that uses an intact homologous template to repair a double strand break (DSB) accurately. It is the predominant pathway in lower eukaryotes, whereas it accounts only for the repair of 10% of DSBs in mammalian cells (reviewed in (Hakem 2008)). HR operates at S and G2 phase of the cell cycle, where a sister chromatid exists, and acts on rapidly dividing cells (Helleday et al. 2007). Furthermore, it fulfills specialized roles; it participates in meiosis and the repair of DNA interstrand crosslinks, which are highly cytotoxic DNA lesions (reviewed in (Scharer 2003)). The whole HR process is summarized in Figure 1.

2.7 Non Homologous End Joining (NHEJ)

Non Homologous End Joining (NHEJ) is the predominant pathway for repair of DSBs in higher eukaryotes (Kanaar et al. 2008). It is a conceptually simple pathway that involves the religation of broken ends and as the DNA ends may be damaged, this mode of repair is not necessarily accurate (Lieberman 2008). NHEJ is more important in quiescent or terminally differentiated cells and in G1 phase of the cell cycle. It also plays a crucial role in the generation of diversity in the immune system in V (D) (J) recombination and in telomere maintenance (reviewed in (Hakem 2008)). The NHEJ mechanism is illustrated in Figure 1.

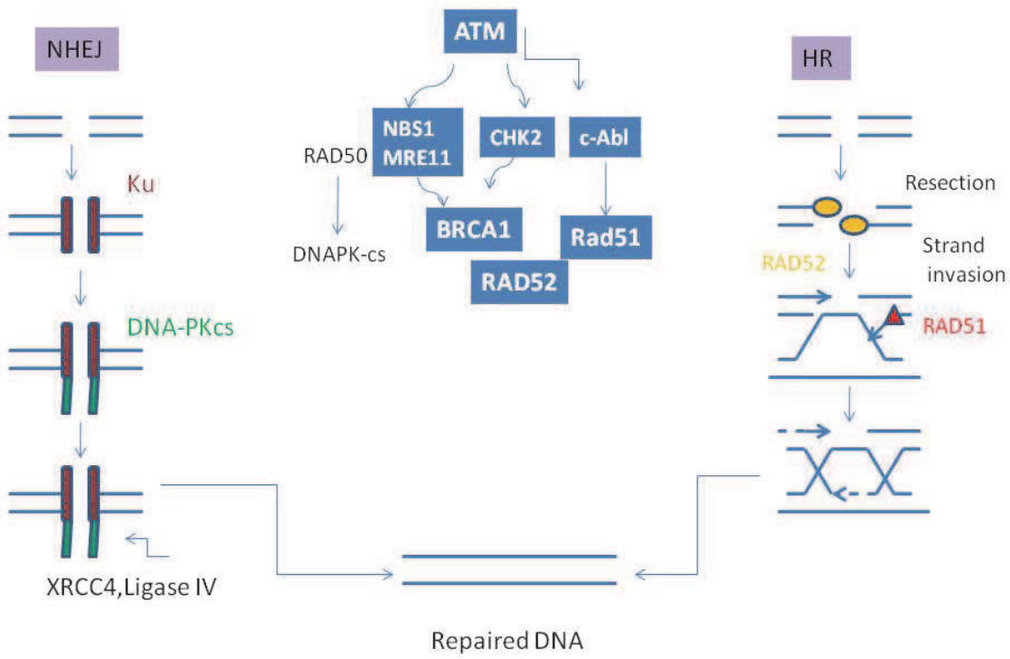


Fig. 1. Model for DSB initial response and repair. Initial recognition of DSB is performed by various sensor proteins (ATM, MRN complex, BRCA1, RAD51, DNA-PKcs). A DSB is repaired either by NHEJ or HR. In NHEJ, the heterodimer Ku70/80 binds to DSB and recruits DNA-PKcs, which promotes ends juxtaposition. Gaps are filled by polymerases μ or λ and nicks are sealed by ligase complex (Ligase IV, XRCC4). In HR, after resection of DSB, Rad51 forms a nucleoprotein filament. Then, a strand-exchange reaction generates a joint molecule between the damaged and the undamaged DNA. Then, repair synthesis is performed by DNA polymerases δ/ε.

Design and nomenclature of Single Nucleotide Polymorphisms (SNPs)

Single Nucleotide Polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide — A, T, C, or G — in the genome differs between members of a biological species or paired chromosomes in an individual (Stenson et al. 2009). It indicates a non disease-causing change or a change found at a frequency of 1% or higher in the population. SNPs may fall within coding sequences of genes, non-coding regions of genes, or in the intergenic regions between genes. SNPs within a coding sequence do not necessarily change the amino acid sequence of the protein that is produced, due to degeneracy (redundancy) of the genetic code (den Dunnen and Antonarakis 2003).

The nomenclature for SNPs can be confusing: several variations can exist for an individual SNP and consensus has not yet been achieved. One approach is to write SNPs with a prefix showing the wild-type and altered nucleotide or amino acid. Variants can be described either at the DNA, RNA or protein level (Ogino et al. 2007).

Descriptions at DNA level refer to a single nucleotide substitution designated by a ">"-character that indicates the change from the wild type to the altered nucleotide. Description is made in relation to a coding or genomic reference sequence. Regarding nucleotide numbering, when a coding reference is used, nucleotide 1 is the A of the ATG-translation initiation codon and the nucleotide 5' of the ATG-translation initiation codon is -1; the previous -2 etc. When a genomic reference is used, nucleotide numbering is purely arbitrary and starts with 1 at the first nucleotide of the database reference file (den Dunnen and Antonarakis 2000, 2003). For example, SNP RAD51 135 G>C, denotes that at nucleotide 135 a G is changed to a C. On the other hand, SNP RAD50 -38C>T denotes a C to T substitution 38 nucleotides 5' of the ATG translation initiation codon.

Descriptions at RNA and protein level are often deduced and not based on experimental evidence. Sequence changes at RNA level are basically described like those at the DNA level, with a few modifications. Description starts with the nucleotide number, followed by the nucleotide (in lower case), for example 78 u>a. In this chapter, none of the SNPs is described at RNA level. Descriptions at protein level start with the amino acid, followed by its number and the altered amino acid (den Dunnen and Antonarakis 2000, Ogino et al. 2007). For example, SNP XRCC1 Arg194Trp indicates a change of amino acid Arginine 194 to Tryptophan.

Finally, frequently SNPs are reported in relation to their reference SNP ID number, which is assigned to them from the Single Nucleotide Polymorphism Database (dbSNP). dbSNP is a free public archive for genetic variation within and across different species developed and hosted by the National Center for Biotechnology Information (NCBI) in collaboration with the National Human Genome Research Institute (NHGRI) (Wheeler et al. 2007). When submitted, SNPs receive a reference SNP ID number ("rs#"; "refSNP cluster"). For example, XRCC4 rs13178127 refers to the SNP of the gene XRCC4 that has received the reference ID number rs13178127.

3. DNA repair deficiency related to hematological malignancies

Below, we summarize the existing data concerning abnormalities of DNA repair pathways in the most common hematological malignancies.

3.1 Acute Myeloid Leukemia (AML)

Acute Myeloid Leukemia (AML) is a group of marrow-based neoplasms that have clinical similarities but distinct morphologic, immunophenotypic and cytogenetic features (Monzo

et al. 2006). Clinical features are similar at any age and are the result of suppression of normal marrow elements by malignant blasts.

Although many environmental and genetic factors have been suggested to play a role in AML pathogenesis, the mechanism still remains uncertain. Through the last years many studies have focused on indentifying genetic differences that could contribute to a patient's predisposition to develop AML. These differences could be in part attributed to polymorphisms that lead to increased or decreased activity of the encoded genes; and DNA repair genes are attractive candidates for studies, since their ineffectiveness causes chromosomal instability. This is further supported by the higher incidence of AML in patients with syndromes characterized by defective DNA repair (Schwartz and Cohen 1988). So far, several polymorphisms have been associated with an increased risk of developing AML, such as polymorphisms of Homologous Recombination genes XRCC3 Thr241Met and RAD51 135G>C (Voso et al. 2007). In another study, these two polymorphisms have been reported to have a synergistic effect on AML development (Seedhouse et al. 2004). In addition, XRCC3 Thr241Met has been found to specifically increase the risk of inv(16)/t(16;16) AML and to be an independent poor prognostic factor for this AML subtype, since it reduces disease free survival in patients that achieved complete remission (CR) (Liu L. et al. 2011). This is an interesting finding, since it could help us substratify patients with inv (16)/t (16; 16) AML, which has favorable prognosis. On the other hand, RAD51 135 G>C has also been associated with a decreased risk of AML (Rollinson et al. 2007). In this study, the authors claim that this polymorphism results in overexpression of RAD51 that might modulate HR in favor of the cells, protecting them from aberrant DNA repair events. Among other polymorphisms, XPD 2251A>C has been associated with increased risk of developing AML, mainly attributed to the C allele (Shi et al. 2011).

It is also known that patients with AML have different response rates to the same treatment agents. Although administration of Ara-C, in conjunction with an anthracycline, is the cornerstone of therapy, the question of the best therapy for AML in first remission remains unanswered, and perhaps it could be stratified according to certain features. In this regard, several studies have focused on finding polymorphisms that have impact on the effects of chemotherapy and as a result, clinical outcome. It is known that good response to chemotherapy is usually associated with low DNA repair capacity, whereas chemoresistance is usually associated with a high DNA repair activity. Although there has been much effort on identifying DNA repair polymorphisms that could predict chemotherapy effectiveness in order to allow appropriate selection of drugs in specific patients, the existing results are of no clinical use and are sometimes contradictory. For example, polymorphism XPD Lys751Gln has been correlated with reduced risk of resistant disease (RD) due to an increased chemotherapy response rate (Kuptsova et al. 2007). However, in another study, the same polymorphism has also been associated with poor response to chemotherapy and decreased survival in patients with intermediate risk AML and normal cytogenetics (Strom et al. 2010). Of course, this controversy might be explained by different patient groups involved in these studies and it could be claimed that XPD Lys751Gln is a predictor of poor response to front line chemotherapy only in patients with normal karyotype. Among other polymorphisms, XPD Asp312Asn is reported to have a positive impact on drug effectiveness (Kuptsova et al. 2007) and XPC Ala499Val has been associated with decreased overall survival in AML patients with normal karyotype (Strom et al. 2010). Furthermore, in a study that included 110 AML patients, patients with XPA genotype -4A>G have been shown to have a higher frequency of chemoresistant disease

when compared to wild type carriers (30% vs. 6, 5 % genotype AA) (Monzo et al. 2006). Finally ATM variant 4138C>T has been associated with poor response to chemotherapy in Chinese population (Shi et al. 2011); however this finding is difficult to be confirmed in European studies, due to its low penetrance (Choudhury et al. 2008, Johnson et al. 2007).

Apart from the above polymorphisms, several studies implicate BRCA1 (involved in initial recognition of a double strand break) and BRCA2 gene (involved in Homologous Recombination) deficiencies in AML pathogenesis. Scardocci et al. observed that 32% of primary AML samples present with hypermethylated BRCA1 (Scardocci et al. 2006). Although this finding has not been confirmed in other studies (Bianco et al. 2000, Esteller et al. 2001), a meta-analysis performed in 2007 which reviewed risks for hematological malignancies associated with mutations in BRCA1/2 pathway, showed that defects in this pathway increase the risk for a subset of AML that are related to gene rearrangements (Friedenson 2007). Consequently, it could be hypothesized that BRCA1/2 pathway's proper function is essential to prevent a group of leukemias. Consistent with these data is the observation that Fanconi anemia patients with biallelic mutations in BRCA2 present with a high risk of AML (Wagner et al. 2004).

Recent evidence suggests a role of error-prone Non Homologous End Joining (NHEJ) in AML development. In preclinical studies, sequencing of breakpoint junctions in AML cells has revealed microhomologous sequences and small deletions, indicative of NHEJ repair (Gillert et al. 1999, Olive 1998, Wiemels et al. 2000, Wiemels et al. 2002, Yoshida et al. 1995). This increased NHEJ activity must, however, be confirmed in other studies.

Regarding Mismatch Repair (MMR) Mechanism, published data in AML are somewhat conflicting. Although there are studies demonstrating increased rates of microsatellite instability in certain types of leukemia (mostly therapy-related AML and myelodysplastic syndromes (Ben-Yehuda et al. 1996, Kaneko et al. 1995)), most reports have described little or no evidence of deficient MMR in AML (Boyer et al. 1998, Sill et al. 1996, Tasak et al. 1996). However, while none of these studies focused on MMR deficiency in different stages of AML, in 2008 Mao et al. showed that more than 30% of AML patients presented with mutations in MMR genes and that MMR deficiency was higher in patients with relapsed/ refractory AML (Mao et al. 2008). Authors suggest the possibility of leukemia relapse generating from leukemic cells defective in MMR that have survived chemotherapy and present the minimal residual disease (Mao et al. 2008).

In conclusion, many polymorphisms of DNA repair genes have been associated with individual susceptibility to AML, as well as pathogenesis and sensitivity to chemotherapy. The precise functional mechanism of their effect remains to be determined; however results strongly support the importance of considering them as prognostic factors or indicators of treatment strategy. Hopefully, further studies will elucidate their role with the view to use them in clinical setting.

3.2 Acute Lymphoblastic Leukemia (ALL)

Acute Lymphoblastic Leukemia (ALL) is a malignant disease characterized by accumulation of immature lymphoblasts. It is the most common leukemia in children, accounting for 70-80% of all childhood leukemias. In the contrast, ALL accounts for 15-20% of leukemias in adults (Faderl et al. 1998).

There is strong evidence that acquired genetic changes are central to the development of ALL. Polymorphisms of DNA repair genes have been investigated as potential pathogenetic and prognostic factors. The majority of studies are focused on childhood ALL, due to its

high frequency in children. Several polymorphisms have been implicated, but results are somewhat conflicting, probably because of the different ethnic groups involved in each study. Thus, polymorphism XRCC1 Arg399Gln has been associated with increased risk of childhood ALL, in Indians (Joseph et al. 2005), Chinese (Zhu et al. 2005) and Thais (Pakakasama et al. 2007), but no correlation was found in Mexican (Meza-Espinoza et al. 2009), Brazilian (da Silva Silveira et al. 2009) and Turkish children (Batar et al. 2009). Perhaps this polymorphism has a stronger effect or a higher penetrance in Asian populations. In other studies, it has been proposed that it has a synergistic effect with CYP2E1*5B polymorphism of detoxification enzyme CYP2E1 (Tumer et al. 2010), as well as polymorphism OGG1 Ser326Cys (Stanczyk et al. 2011) in ALL development. Similarly, polymorphism XRCC1 Arg194Trp, has been found to have a protective effect in Thais (Pakakasama et al. 2007), while opposite results have been found in another study (Joseph et al. 2005). Moreover, several XRRC1 haplotypes have been related to ALL; haplotype B, as well as C, have been associated with an increased ALL risk (Meza-Espinoza et al. 2009, Pakakasama et al. 2007).

On the other hand, polymorphisms of Nucleotide Excision Repair genes have also been investigated in ALL in a few studies. XPD Asp312Asn and Lys751Gln polymorphisms, which have been previously associated with AML, have not been found to be correlated with ALL risk (Batar et al. 2009, da Silva Silveira et al. 2009). On the contrary, CC genotype of ERCC18092C>A polymorphism has been suggested to increase susceptibility to ALL in Chinese children (Wang et al. 2006). In the same study, ERCC1 19007G>A was not found to be associated with ALL (Wang et al. 2006).

Regarding Mismatch Repair (MMR) mechanism, most of the existing studies have failed to show an association between MMR deficiency and ALL development (Molenaar et al. 1998, Takeuchi et al. 1997), although preclinical studies have demonstrated MSI in ALL cell lines (Gu et al. 2002, Hangaishi et al. 1997). In addition, no relationship was found between polymorphisms in MMR genes MLH1 and MSH3 and childhood ALL (Mathonnet et al. 2003), although a combined effect was demonstrated with CYP2A1*2A and CYP2E1*5 polymorphisms of detoxification enzymes, suggesting a possible interaction between DNA repair enzymes and detoxification enzymes in childhood ALL. In addition, in another study that evaluated the risk of childhood ALL and the presence of variants in DNA repair enzymes in children exposed to diagnostic X-rays, hMLH1 was found to protect against X-ray exposure (Infante-Rivard et al. 2000).

Finally, it is worth mentioning that a positive correlation has been found between polymorphism 8360G>C in NBS1 gene (component of MRN complex) and ALL. It is interesting that this study included ALL patients from different ages, but results are potentially questionable, since the study was limited to a small size group of Chinese population (Jiang et al. 2011).

In summary, although many polymorphisms have been associated with ALL, investigation remains still at an early stage. Further studies are needed in order to be able to draw definite conclusions for the potential use of polymorphisms for the stratification of patients in different prognostic and treatment groups.

3.3 Myelodysplastic Syndromes (MDS)

Myelodysplastic syndromes (MDS) represent a spectrum of stem cell malignancies that manifest dysplastic and ineffective hematopoiesis, which is associated with a variable risk of transformation to AML. They usually arise de novo with the risk of developing MDS increasing proportionally to age (Doll and List 1989, Noel and Solberg 1992).

It is known that genetic lesions in hematopoietic progenitor cells play a major role to their malignant transformation and there is accumulating evidence that genetic factors modify a person's cumulative risk to MDS (Janssen et al. 1989). It has also been suggested that disease progression of MDS to AML is attributed to accumulation of mutations that cause defects in DNA repair (Rowley 1999); as a consequence, most of the existing studies are interested in identifying whether DNA repair polymorphisms implicated in AML are also involved in MDS. However, only one study found a positive correlation between polymorphism RAD51 135G>C and MDS risk; and it is difficult to interpret this result, since the study is limited to a Chinese population (Li et al. 2010). All other studies did not show any association between DNA repair polymorphisms and MDS (Baumann Kreuziger and Steensma 2008, Fabiani et al. 2009). This contradiction might be interpreted by the fact that these polymorphisms have been associated with *de novo* AML, whose pathogenesis is a different molecular procedure compared to MDS.

Finally, in an effort to examine a possible role of Non Homologous End Joining (NHEJ) repair mechanism in MDS, we have previously tested the expression of NHEJ protein components in 48 cases of adult de novo MDS (Economopoulou et al. 2009). We reported a significantly lower Ligase IV expression level in MDS patients compared to controls and an association of Ku70 expression with more aggressive disease, suggesting a potential role of these two molecules in MDS pathogenesis and clinical presentation. However, a larger number of cases need to be examined in order to confirm these findings.

3.4 Chronic Myeloid Leukemia (CML)

Chronic Myeloid Leukemia (CML) is a clonal stem cell disorder characterized by increased proliferation of myeloid elements at all stages of differentiation (Champlin and Golde 1985). It is caused by the Bcr-Abl oncoprotein, the product of the t (9;22) chromosomal translocation that generates the Philadelphia chromosome. CML is a multistep disease, which involves a chronic phase (CP) that finally progresses to a blast crisis (BC).

Although imatinib, a selective inhibitor of the ABL kinase, has revolutionized the treatment of CML (Druker et al. 1996), it has not completely eradicated it, and has a poorer response rate in patients with CML and blast crisis (BC) (Oehler et al. 2007). Progression to BC has been associated with the appearance and accumulation of new cytogenetic abnormalities; therefore, there are many studies focusing on transformation to BC pathogenesis. It has been recently found that BCR-ABL transformed cells have an increased level of Reactive Oxygen Species (ROS) that induces numerous double strand breaks (DSBs) (Nowicki et al. 2004). It was also shown that BCR-ABL upregulates error-prone DSB repair pathways (Non Homologous End Joining-NHEJ) rather than the high-fidelity mechanism of Homologous Recombination, promoting mutagenic DSB repair (Nowicki et al. 2004, Salles et al. 2011) . Therefore, it could be suggested that mutagenic DSB repair might provoke chromosomal abnormalities found in the progression to BC (Nowicki et al. 2004). Furthermore, it was recently demonstrated that BCR-ABL increases expression and activation of WRN (involved in NHEJ), which promotes unfaithful repair and protects leukemia cells from apoptosis, resulting in genomic instability (Slupianek et al. 2011).

Moreover, several DNA Repair proteins have been found to be associated with CML and have been suggested to play a potential role in CML-BC pathogenesis. DNA-PKcs has been found to be decreased in BCR-ABL transfected cells, as well as CD34+ cells from CML patients (Deutsch et al. 2001). This reduced expression of DNA-PKcs was correlated with DNA repair deficiency, that might contribute to genetic instability found in BC (Deutsch et

al. 2001). It could be therefore suggested that low expression of DNA-PKcs is involved in progression to CML-BC. Among other proteins, XPB has been isolated from BCR domain and it has been shown that continuous interaction with BCR-ABL provokes XPB deficiency and chromosomal instability (Takeda et al. 1999). Finally, hMSH3 Mismatch Repair protein has been found to be reduced in CML patients (Inokuchi et al. 1995). However, we can't ignore that the percentage of CML patients with reduced hMSH3 expression in that study was very high (90%), but the number of CML samples examined was small (10). Given the fact that the finding has not been confirmed in other studies, its reliability is questionable.
Abnormalities of DNA repair components and their impact on myeloid malignancies are summarized in Table 1.

3.5 Non Hodgkin's Lymphoma (NHL)

Non Hodgkin's Lymphoma (NHL) includes multiple neoplastic disorders of the lymphoid system with overlapping features. They most commonly derive from mature B-cells of germinal center origin. Clinical presentation is highly variable and depends on a number of factors; however NHL share a number of common clinical and pathologic features.
DNA repair has a pivotal role in NHL development. Defects in DNA repair can lead to the development of chromosomal aberrations, a hallmark of lymphoma (Palitti 2004). This is further supported by the fact that several hereditary syndromes, including Ataxia telangiectasia and Nijmegen breakage syndrome are characterized by defective DNA repair and high occurrence of lymphoma. Among studies focused on DNA repair polymorphisms and their impact on NHL, three parallel studies conducted in the US and Australia have reported different or contradictory results. In the first one, DNA ligase IV (Lig4) 9 I variant allele has been found with lower frequency in NHL patients, including follicular lymphoma (FL) and Diffuse Large B-Cell Lymphoma (DLBCL) patients, compared to controls (Hill et al. 2006). This finding is in accordance with another case control study, where LIG4 9 I/I homozygotes had a 3 fold reduced NHL risk (Roddam et al. 2002). Among other polymorphisms examined, RAG1 K820R variant allele (involved in V (D) J recombination), BRCA2 Arg372His genotype and XRCC1 Arg194Trp were associated with an increased risk of NHL (Hill et al. 2006). However, the latter has not been confirmed in other studies that evaluated the impact of XRRC1 polymorphisms in NHL (Liu J. et al. 2009, Smedby et al. 2006). Finally, WRN V114I variant was found to be associated with a decreased risk of NHL (Hill et al. 2006). In contrast, in the second study conducted in Connecticut, these results were not confirmed. However, a negative association was demonstrated between NHL and another WRN polymorphism, Cys1367Arg, suggesting a protective role of WRN in NHL (Shen et al. 2006). On the other hand, polymorphism XPG Asp1104His has been for the first time correlated with elevated NHL risk, including DLBCL and T-cell lymphomas (Shen et al. 2006). Finally, the third study which included patients from Australia, found no association between the above polymorphisms and NHL (Shen et al. 2007). However, it has been found that MGMT SNPs Ala143Val and Lys178Arg are associated with elevated NHL risk, including FL, DLBCL and MALT lymphoma (Shen et al. 2007).
Interestingly, a pooled investigation of genetic variation in 27 DNA repair genes based on the three above studies, revealed different results (Shen et al. 2010). Among the examined SNPS, BLM rs441399 was significantly associated with follicular lymphoma and XRCC4 rs13178127 was correlated with NHL overall (Shen et al. 2010). Of note, products of BLM and XRCC4 genes are both involved in DSB repair and they both interact with Ligase IV.

Moreover, in the same study, ERCC3 rs4150506 was associated with reduced risk for marginal zone lymphoma (MZL) (Shen et al. 2010).

Similarly, Worrillow et al. (Worrillow et al. 2009) analyzed polymorphisms in XPD gene, in a UK population study that involved 747 NHL cases. This is the largest study assessing the impact of XPD polymorphisms on NHL. There were no statistically significant case control differences in the distribution of XPD polymorphisms. However, a decreased risk of diffuse large B-cell lymphoma was observed in variants for XPD Lys751Gln. This finding has been previously reported (Shen et al. 2006). Furthermore, XPD 156 A>C was found to be associated with an increased risk of follicular lymphoma (Worrillow et al. 2009).

Similarly, Rollinson et al. (Rollinson et al. 2006) studied the haplotypic variation of tri-complex MRE11-RAD50-NBS1 and its relationship with NHL risk. The main findings of the study were a protective effect for MRE11 rs601341 variant in follicular lymphoma and for the MRE11 GCTCA haplotype in diffuse large B-cell lymphoma (DLBCL), suggesting a possible role of protein MRE11 in DLBCL pathogenesis. No altered NHL risk associated with haplotypes of NBS1 and RAD50 was observed in this study. Another similar study was performed by Schuetz et al (Schuetz et al. 2009). The authors suggest an association of a RAD50 SNP -38C>T with Mantle Cell Lymphoma (MCL), but the low incidence of both the SNP and MCL make these data questionable. No association was observed between NBS1 haplotypes and NHL (Schuetz et al. 2009). In contrast to the previous study, this one failed to show any correlation of MRE11 rs601341 variant with NHL, but the authors propose that this disparity is due to the fact that the part of intron where rs601341 was located was not sequenced.

Additionally, ATM protein, also involved in double strand break response, has been associated with NHL. Schaffner et al. (Schaffner et al. 2000) reported inactivation of both alleles of ATM gene in a high proportion of patients with Mantle Cell Lymphoma (MCL), suggesting that ATM functions as a tumor suppressor gene in MCL. This finding has been confirmed in subsequent studies that provide evidence for somatic mutations in ATM in MCL (Fang et al. 2003, Taylor et al. 1996). On the other hand, ATM has been associated with NHL of B-origin (B-NHL) clinical outcome, since deletion of one ATM allele has been found to strongly influence B-NHL survival (Vorechovsky et al. 1997). However, another study reported contradictory results claiming that common variants in ATM do not influence NHL susceptibility (Sipahimalani et al. 2007). The authors suggest that individuals with common ATM variants are phenotypically normal and that only rare variants could possibly influence NHL susceptibility. The role of rare ATM variants in NHL remains to be elucidated.

Among other DNA repair proteins, it is worth mentioning the role of Nucleotide Excision Repair component hHR23B as an apoptosis- associated protein in Burkitt Lymphoma (Vogel et al. 2005).

Finally, the role of Mismatch Repair (MMR) pathway in NHL has also been investigated, although limited published data exist. Kotoula et al. (Kotoula et al. 2002) described a low expression of proteins hMLH1 and hPMS1 in B-cell lymphomas and in Mantle Cell Lymphoma (MCL) of blastoid type compared to normal controls, although in B-Chronic Lymphocytic Leukemia and Mantle cell Lymphoma of centrocyte-like type the expression of MMR genes remained intact. The small sample size and the heterogeneity of the specimens, along with the lack of additional published data that could support the findings, make these data questionable. Furthermore, Morimoto et al. (Morimoto et al. 2005) observed a reduced expression of MMR genes in patients with adult T-cell Leukemia (ATL), supporting a role of

MMR gene inactivation in disease progression and development of ATL. Although the number of patients included in the study is small, the results are promising and give insight for further investigation.

3.6 Hodgkin's Lymphoma (HL)

Hodgkin's lymphoma (HL) is a hematolymphoid neoplasm, primarily of B-cell lineage, with unique molecular, histologic, immunophenotypic and clinical features. The diagnosis of classical HL requires the recognition of Reed-Steinberg cells in an appropriate cellular milieu (Liu A. et al. 2008).

To date, the effect of DNA repair polymorphisms on HL has not been yet thoroughly investigated. However, few studies have tried to assess their role on HL development. In a large study that involved 200 newly diagnosed adult HL patients, a positive association was demonstrated between XRCC1 Arg399Gln and risk of HL (El-Zein et al. 2009). Interestingly, the authors observed that combined analysis of XRCC1/XRCC3 and XRCC1/XPC polymorphisms revealed significant association with increase in HL risk. For example, XRCC3 Thr241Met was associated with an OR of 2.38 when combined with homozygous XRCC1 Arg/Arg genotype. XRCC1 Gln/Gln along with XRCC3 variant led to a 3 fold increased HL risk. Similarly, XRCC1 Arg399Gln together with XPC Lys/Lys was found to significantly increase HL risk. Similar findings were reported in a recent study that evaluated potential gene-gene interaction between DNA repair genes and their contribution to individual susceptibility to HL (Monroy et al. 2011). Polymorphism XRCC1 Arg399Gln was again associated with increased HL risk, as well as polymorphisms XPC Ala499Val, XRCC3 Thr241Met and XRCC1 Arg194Trp. Most importantly, it was observed that HL risk increases as the number of adverse alleles in Base Excision Repair (BER) and repair of double strand breaks (DSBR) increases. Taken together these two studies suggest a potential cooperation between BER and DSBR mechanisms in HL development; however the exact procedure remains to be elucidated.

Furthermore, there is strong evidence that ATM gene is involved in the pathogenesis of HL. The existing data refers to identification of four SNPs of ATM gene with a defective protein activity (Takagi et al. 2004). Consequently, it could be proposed that in the presence of genotoxic stress, these defects might be amplified and lead to accumulation of mutations that may contribute to a malignant phenotype. Similarly, Liberzon at al. showed that variants of ATM were associated with aggressive disease in children (Liberzon et al. 2004). The main limitation of both these studies is the small sample size that consisted only of children. Further investigation is necessary in order to draw safe conclusions.

Finally, it is worth mentioning that a relationship was recently found between telomere shortening and development of second cancers in HL patients (M'Kacher et al. 2007). Telomere dysfunction is linked to DNA repair and probably to decreased Ku70 expression, although further studies are required to elucidate the mechanism of telomere shortening in HL patients.

3.7 Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia (CLL) is the most common form of adult leukemia in the Western hemisphere (Ganster et al. 2009). It is a neoplastic disorder of mature B lymphocytes that is determined by genetic, molecular and environmental factors. The clinical course of CLL is highly variable. There are two groups of patients with diverse

clinical outcomes that are separated by the mutational status of immunoglobulin variable region (IgV) gene (Hamblin et al. 1999).

Although mutation status of IgV gene, as well as acquired chromosomal abnormalities [del(13q), del(11q), del(17p), trisomy 12] have been identified as prognostic factors in CLL, discovery of further prognostic factors would help to predict disease progression among different patient groups. Recently, polymorphism XPD Lys751Gln not only has been found to be associated with CLL development but it also occurred significantly more frequently in high risk patients. In the same study, polymorphisms XRCC1 Arg399Gln and XPF Arg415Gln were similarly positively correlated with cytogenetically high risk CLL patients. In contrast, polymorphism RAD51 135 G>C was associated with low risk CLL. The most important aspect of this study is that it examines the effect of SNPs on cytogenetic aberrations in CLL and suggests that polymorphisms XPD Lys751Gln and XRCC1 Arg399Gln might predict the unfavorable clinical outcome of CLL. Notably, polymorphism XPD Lys751Gln has been previously been described as a negative prognostic factor in acute myeloid leukemia. However, contradictory results were produced in another study, where XPD Lys751Gln was associated with a decreased risk of developing CLL; there was no distribution among different cytogenetic risk subgroups though (Enjuanes et al. 2008). Similarly, XRCC1 Arg399Gln has not been correlated with CLL in previous studies, although there was again no distinction between different subgroups (Enjuanes et al. 2008, Sellick et al. 2008) . These data suggest that individual genetic polymorphisms may predict the clinical outcome of CLL; however, future studies should focus on confirming the results in a larger group of patients, with the view for clinical application.

It is known that one of the therapies used in CLL is treatment with alkylating agents, which is associated with low rates of complete remission. The ability of CLL cells to efficiently repair alkylator-induced DNA damage might explain lack of response to treatment. Therefore, DNA repair may be linked to chemoresistance in CLL (Sampath and Plunkett 2007). There is strong evidence that both HR and NHEJ play an important role in CLL resistance to chemotherapy. For instance, there is evidence that CLL cells exposed to chlorambucil demonstrate an increase in RAD51 foci (Christodoulopoulos et al. 1999). In addition, resistance to alkylating agents has been associated with enhanced HR repair in CLL cells (Aloyz et al. 2004, Bello et al. 2002, Xu et al. 2005). Similarly, a high level of XRCC3 was associated with lack of response of CLL cells to nitrogen mustards (Bello et al. 2002). Furthermore, it has been reported that low levels of Non Homologous End Joining protein component DNA-PKcs is strongly associated with drug sensitivity in CLL cells, whereas increases in DNA-PK activity resulted in increased resistance to neocarzinostatin and chlorambucil (Amrein et al. 2007, Austen et al. 2005). Inhibition of DNA-PKcs (Amrein et al. 2007), as well as dual inhibition of both RAD51 and DNA-PK (Amrein et al. 2011) has been found to induce drug sensitivity in CLL cells. Recently, the effect of DNA-PK inhibitors in CLL cells was investigated in combination with mitoxantrone. Interestingly, DNA-PK inhibitors provoked mitoxantrone cytotoxicity in CLL cells, especially cells with unfavorable cytogenetic anomalies [del(17p) and del(13q)] (Elliott et al. 2011). These findings could be of vital importance regarding CLL treatment, since DNA repair inhibitors could be used as potential therapeutic targets in combination with alkylating agents for a better clinical outcome, especially in high risk CLL.

Finally, association of DNA repair enzymes' abnormalities with CLL prognosis has been the subject of investigation of several studies. ATM has been implicated in CLL, since it has been shown that approximately 14% of patients with untreated CLL harbor deletions of the

long arm of chromosome 11 at the 11q22-23 (ATM) locus, which is associated with poor survival. An explanation could be that since ATM is an upstream regulator of p53, defects in ATM lead to attenuation of p53-dependent apoptosis, which results in a chemo-refractory phenotype. Furthermore, a correlation was described between protein DNA-PKcs component of Non Homologous End Joining and poor prognosis in CLL in terms of enzyme over-expression in del (17p) and del (11q) unfavorable CLL cases (Willmore et al. 2008). In the same study, high DNA-PKcs levels predicted for reduced treatment-free survival. These findings suggest that DNA-PKcs might contribute to disease progression in CLL, possibly by enhancing error-prone Non Homologous End Joining activity.

3.8 Multiple Myeloma (MM)

The diagnosis of multiple myeloma (MM) requires 10% or more plasma cells on bone marrow examination, M protein in the serum and/or urine (except in patients with true non-secretory myeloma) and evidence of end-organ damage (hypercalcaemia, renal insufficiency and anemia or bone lesions) secondary to the underlying plasma cell disorder. Almost all patients are thought to evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS) (Kyle and Rajkumar 2004). Genetic instability is a prominent feature of MM, since malignant plasma cells display aneuploidy and complex cytogenetics associated with poor prognosis (Calasanz et al. 1997, Rajkumar et al. 1999, Smadja et al. 2001). Two pathways are considered important for disease progression; hyperploid MM involves trisomies of several chromosomes, whereas non-hyperploid MM is characterized by translocations in immunoglobulin heavy chain locus at 14q32 (Bergsagel and Kuehl 2005, Fonseca et al. 2004, Ho et al. 2001). The latter events represent aberrant class switch recombination (CSR), a process that normally alters immunoglobulin isotype with the maturation of immune response (Fenton et al. 2002, Liebisch and Dohner 2006).

Given the fact that CSR requires formation of double stand breaks, the role of Homologous Recombination (HR) and Non Homologous End Joining (NHEJ) in MM pathogenesis has been investigated in many studies. Among DNA repair polymorphisms, XRCC4 rs963248 and rs1051685 Ku80 have been found in a higher frequency in MM patients compared to controls (Hayden et al. 2007). At a protein level, XRCC4 was also recently found to be overexpressed in MM (Roddam et al. 2010) Furthermore, recently, protein Ku80 has been associated again with MM, since it was demonstrated that Ku80/Ku70 are translocated to human MM cells surface and that this localization has functional implications which could contribute to MM pathogenesis (Tai et al. 2002).

Homologous Recombination (HR) has also been investigated in MM. Rad50 has been recently found to be overexpressed in MM patients (Roddam et al. 2010). In another study by Shammas et al. model MM cell lines were used in order to evaluate the molecular mechanisms of genetic instability and progression in malignancies (Shammas et al. 2009). An elevated HR activity is reported in MM cells, which leads to mutations. The authors show that inhibition of HR activity by siRNAs leads to reduction of genetic changes. Therefore, we could presume that HR can be targeted not only for prevention of disease progression, but also for therapy improvement. In another study focused on assessing the role of NHEJ in MM phenotype, authors observed that DSBs, when induced in MM cell lines, exhibited corrupt NHEJ (Yang et al. 2009). Interestingly, with the use of DNA-PK inhibitor was used, NHEJ process was suppressed and DNA ends were processed by intact

HR. This finding suggests that deregulated DSB repair in MM might contribute to complex chromosomal aberrations that, as mentioned above, is typical feature of the disease.
Apart from DSB repair, Mismatch Repair deficiency in MM has been investigated in several studies. Microsatellite instability has been reported in MM patients (Timuragaoglu et al. 2009, Velangi et al. 2004) and has been associated with more aggressive forms of the disease (e.g. plasma cell leukemia-PCL) (Velangi et al. 2004). On the other hand, Martin et al. (Martin et al. 2006) examined the methylation status and expression of enzymes MGMT and hMLH1 in 44 cases of plasma cells disorders [(Multiple Myeloma, Monoclonal Gammopathy of Undetermined Significance (MGUS), Plasma Cell Leukemia (PCL)]. Protein hMLH1 was found to be underexpressed in 50% of cases of MM, but not in patients with MGUS, whereas hMLH1 gene promoter was hypermethylated in 10% patients with MM but not in cases with MGUS. This finding suggests that inactivation of hMLH1 could be implicated in the evolution of MGUS to MM. On the contrary, 33% of MGUS and 44% MM patients had lost the MGMT expression, suggesting that MGMT deficiency is an initial alteration in plasma cell disorders.
Additionally, Nucleotide Excision Repair (NER) enzymes and have been associated with MM. Peng et al. reported epigenetic silencing of NER protein XPD in MM cells that was found to promote clonal expansion of MM cells (Peng et al. 2005). As a consequence, it might contribute to MM pathogenesis. NER has also been studied in the context of autologous bone marrow transplantation (ASCT) in MM. It has been observed that the combination of variant alleles of NER proteins XPD K75Q and XRCC3 T241M correlates with prolonged time to treatment failure in MM patients treated with ASCT (Vangsted et al. 2007). This finding is very important, since polymorphisms in XPD and XRCC3 could potentially predict the outcome in MM patients undergoing ASCT.
Finally, there is recent evidence that DNA repair polymorphisms are related to treatment response rate (RR) in MM. In a study conducted in Spain, it was found that polymorphisms ERCC1 rs735482 and Ku80 rs1051685 were associated with higher RR and longer overall survival in patients with relapsed/refractory myeloma treated with thalidomide (Cibeira et al. 2011). Similarly, RR was better in MM patients with SNPs in ERCC5 rs17655 (Cibeira et al. 2011). Although sample size is relatively small and belongs to a specific group of patients, this study provides very useful information, which, if confirmed in other studies, could be used in clinical practice to predict favorable outcome in relapsed myeloma.
Abnormalities of enzymes involved in DNA repair mechanisms and their influence on hematological malignancies are summarized in Table 1.

4. Conclusions

Genomic instability is the hallmark of all hematological malignancies. Since DNA repair mechanisms are responsible for correcting DNA damage and preserving genomic integrity, it is obvious that abnormalities of these mechanisms are strongly related to hematological cancers. Mutations and polymorphisms of DNA repair genes are associated with alteration of an individual's susceptibility to malignancy. In addition, they are related to prognosis, drug resistance and clinical outcome and represent potential targets for therapy.
We have presented the existing published data that show association of DNA repair mechanisms with the most common myeloid and lymphoid malignancies. Many studies have focused on investigation of the role of Base Excision Repair, Nucleotide Excision Repair, Non Homologous End Joining and Homologous Recombination in hematological

MALIGNANCY	DEFECTS
AML	NER: - XPDGlu751C/Asp312G →↓ risk of RD - XPDAsp312Asn→↓ risk of RD/↓survival in AML with normal karyotype - XPD Lys751Gln A>C→ ↑ AML risk -XPC Ala499Val→↓OS in normal karyotype - XPA 4A>GGG→ chemoresistant disease, ↓OS BER: - XRCC3 Thr241Met→ ↑ AML risk, especially inv(16)/t(16;16) AML HR: -Rad51G135C→2x ↑ or ↓ AML risk? - Rad51-135-172-C haplotype →↓ AML risk NHEJ: - ↑ NHEJ activity and repair infidelity DSBR: - ATM variant 4138CT→ poor response to chemotherapy in Chinese -hypermethylation of BRCA1 MMR: -MMR deficiency in relapsed/refractory AML.
ALL	BER: - XRCC1 194Trp allele → ↓ risk ALL in Thais, ↑ risk in Indians - XRCC1 399Gln →↑ risk of ALL in Indians, Chinese, Thais - XRCC1 haplotypes B&C→↑ risk of ALL NER: - ERCC1 8092C>A CC genotype→↑ risk of ALL in Chinese DSBR:- E185Q in NBS1→ ↑ risk of ALL MMR: - MLH1 Ile-219/Ile-219+ CYP2A1*2A/ +GSTM1/ +CYP2E1*5→↑ risk of ALL
MDS	HR: -RAD51-G135C→↑ risk of MDS? NHEJ:- ↓ Ligase IV expression in MDS vs. controls, ↑ Ku70 expression→ aggressive disease
CML	NER: -XPB binds to BCR domain →dysfunction of XPB → role in BC? DSBR: -BCR/ABL(+) cells→ ↑ DSBs, high mutation rate in HR/NHEJ→genomic instability HR:- DNA-PKcs expression in hematopoietic cells transfected with BCR/ABL/ CD34+ cells from CML patients MMR:- hMSH3 ↓ in MMR
NHL	DR:- MGMT Ile143Val and MGMT Lys178Arg→↑ risk of NHL (FL,DLBCL,MCL,T-Cell Lymphomas) BER: - XRCC1 Arg194Trp→ ↑ risk of NHL,↓ risk of DLBCL NER: - XPD K751QCC→↓ risk of DLBCL -XPD R156R→↑ risk of FL -XPG Asp1104His→↑ risk of NHL - hHR23B→Burkitt lymphoma? DSBR: -Loss of ATM in MCL -MRE11 GCTCA→↓ risk of DLBCL -MRE11 rs601341→↓ risk of FL - BLM rs441399→↑ risk of FL - BRCA2 372 H/H→ ↓ risk of NHL (FL & DLBCL) - RAG1 820R→↑ risk of NHL

	NHEJ: -.Ligase 9I var allele→↓ risk of NHL (FL & DLBCL) -WRN V114l variant→↓ risk of NHL -WRN Cys1367Arg→↓ risk of NHL MMR: - hMLH1, hPMS1→↓ risk for B-NHL and MCL blastoid type -MMR genes inactivation→ role in ATL disease progression
HL	BER:- XRCC1 Arg399Gln→↑ risk for HL -XRCC3 Thr241Met, XRCC1 Arg194Trp→↑ risk for HL - polymorphisms XRCC1/XRCC3& XRCC1/XPC→↑ risk for HL DSBR:- SNPS of ATM with defective function
CLL	BER: -XRCC1 399Gln→ ↑in CLL with unfavorable prognosis NER: -XPD Lys751Gln→↑ in CLL with unfavorable prognosis -XPF Arg415Gln→ ↑ in CLL with unfavorable prognosis DSBR: Inactivation of ATM HR:- Rad51 G135C→↑ in CLL with favorable prognosis -.↑ Rad51 foci in CLL exposed to chlorambucil→ resistance to chlorambucil ? -↑ HR activity in CLL cells exposed to alkylating agents→ resistance to alkylating agents NHEJ:- ↓ DNA-PKcs expression→ chemosensitivity -↑ DNA-PK activity→ resistance to chlorambucil -↑ DNA-PKcs expression in CLL patients with poor prognosis→ disease progression?
MM	DR: -MGMT ↓/hypermethylated in MM NER: -XPD K75Q→↑ prolonged TTR in MM patients with ASCT -ERCC1 rs735482→↑ RR and OS in relapsed/refractory MM HR: - Rad50 overexpresion in MM patients - ↑ HR activity in MM cell lines -XRCC3 T24↑ 1M→↑ prolonged TTR in MM patients with ASCT NHEJ: -XRCC4 rs96248 Allele A→↑ risk of MM -Overexpession of XRCC4 -Ku80 rs1051685 GG→↑ risk for MM - Corrupt NHEJ in MM cell lines - Ku80 rs1051685→↑ RR and OS in relapsed/refractory MM

DR= Direct Repair, BER= Base Excision Repair, NER= Nucleotide Excision Repair, MMR= MisMatch Repair, DSBR= Double Strand Break Repair, HR= Homologous Recombination,
NHEJ= Non Homologous End Joining, AML= Acute Myeloid Leukemia, ALL= Acute Lymphoblastic Leukemia, MDS= Myelodysplastic Syndromes, CML= Chronic Myeloid Leukemia,
NHL= Non Hodgkin Lymphoma, FL= Follicular Lymphoma, DLBCL= Diffuse Large B- Cell Lymphoma, MCL= Mantle Cell Lymphoma, ATL= Adult T- cell Leukemia,
HL= Hodgkin's Lymphoma, , CLL= Chronic Lymphocytic Leukemia,
MM= Multiple Myeloma, MGUS= Monoclonal Gammmopathy of Undetermined Significance,
TTR= Time to Treatment Failure, ASCT= Autologous Stem Cell Transplantation,
RD= Resistant Disease, BC= Blast Crisis, OS=Overall Survival

Table 1. Defects of DNA repair mechanisms in hematological malignancies

diseases, whereas few data is reported regarding the impact of Direct Repair and Mismatch Repair on these malignancies. The most commonly studied diseases are acute myeloid leukemia and Non Hodgkin's Lymphoma. Among all the data reviewed, none has clinical

application yet, therapeutic or prognostic. Further analysis of DNA repair pathways alterations is essential in order to elucidate their pathogenetic role in hematological malignancies and establish alternative therapeutic options that could be used in a clinical level, in order to help improve prognosis and survival of patients with hematological cancers.

5. Abbreviations

AGT/MGMT	O^6-alkylguanine transferase
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
ATL	Adult T-cell Leukemia
ASCT	Autologous Stem Cell Transplantation
BC	Blast crisis in chronic myeloid leukemia
BER	Base Excision Repair
B-NHL	Non Hodgkin's Lymphoma of B-origin
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
CP	Chronic Phase in chronic myeloid leukemia
CR	Complete Remission
CSR	Class Switch Recombination
dbSNP	Single Nucleotide Polymorphism Database
DDR	DNA Damage Response
DLBCL	Diffuse Large B-Cell Lymphoma
DR	Direct Repair
DSB	Double Strand Break
FL	Follicular Lymphoma
GG-NER	Global Genome Nucleotide Excision Repair
HL	Hodgkin's Lymphoma
HR	Homologous Recombination
IgV	Immunoglobulin Variable region
LP-BER	Long Patch Base Excision Repair
MCL	Mantle Cell Lymphoma
MDS	Myelodysplastic Syndromes
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
MMR	Mismatch Repair
MSI	Microsatellite Instability
MZL	Marginal Zone Lymphoma
NCBI	National Center for Biotechnology Information
NER	Nucleotide Excision Repair
NHEJ	Non Homologous End Joining
NHGRI	National Human Genome Research Institute
NHL	Non Hodgkin's Lymphoma
OR	Odd Ratio

OS	Overall Survival
PCL	Plasma-Cell Leukemia
RD	Resistant Disease
ROS	Reactive Oxygen Species
RR	Response Rate
SNP	Single Nucleotide Polymorphism
SP-BER	Short-Patch Base Excision Repair
TC-NER	Transcription Coupled Nucleotide Excision Repair
TTR	Time to Treatment Failure

5. References

Aloyz R, Grzywacz K, Xu ZY, Loignon M, Alaoui-Jamali MA, Panasci L. 2004. Imatinib sensitizes CLL lymphocytes to chlorambucil. Leukemia 18: 409-414.

Altieri F, Grillo C, Maceroni M, Chichiarelli S. 2008. DNA damage and repair: from molecular mechanisms to health implications. Antioxid Redox Signal 10: 891-937.

Amrein L, Loignon M, Goulet AC, Dunn M, Jean-Claude B, Aloyz R, Panasci L. 2007. Chlorambucil cytotoxicity in malignant B lymphocytes is synergistically increased by 2-(morpholin-4-yl)-benzo[h]chomen-4-one (NU7026)-mediated inhibition of DNA double-strand break repair via inhibition of DNA-dependent protein kinase. J Pharmacol Exp Ther 321: 848-855.

Amrein L, Davidson D, Shawi M, Petruccelli LA, Miller WH, Jr., Aloyz R, Panasci L. 2011. Dual inhibition of the homologous recombinational repair and the nonhomologous end-joining repair pathways in chronic lymphocytic leukemia therapy. Leuk Res.

Austen B, Powell JE, Alvi A, Edwards I, Hooper L, Starczynski J, Taylor AM, Fegan C, Moss P, Stankovic T. 2005. Mutations in the ATM gene lead to impaired overall and treatment-free survival that is independent of IGVH mutation status in patients with B-CLL. Blood 106: 3175-3182.

Bakkenist CJ, Kastan MB. 2004. Initiating cellular stress responses. Cell 118: 9-17.

Batar B, Guven M, Baris S, Celkan T, Yildiz I. 2009. DNA repair gene XPD and XRCC1 polymorphisms and the risk of childhood acute lymphoblastic leukemia. Leuk Res 33: 759-763.

Baumann Kreuziger LM, Steensma DP. 2008. RAD51 and XRCC3 polymorphism frequency and risk of myelodysplastic syndromes. Am J Hematol 83: 822-823.

Bello VE, Aloyz RS, Christodoulopoulos G, Panasci LC. 2002. Homologous recombinational repair vis-a-vis chlorambucil resistance in chronic lymphocytic leukemia. Biochem Pharmacol 63: 1585-1588.

Ben-Yehuda D, et al. 1996. Microsatellite instability and p53 mutations in therapy-related leukemia suggest mutator phenotype. Blood 88: 4296-4303.

Bergsagel PL, Kuehl WM. 2005. Molecular pathogenesis and a consequent classification of multiple myeloma. J Clin Oncol 23: 6333-6338.

Bianco T, Chenevix-Trench G, Walsh DC, Cooper JE, Dobrovic A. 2000. Tumour-specific distribution of BRCA1 promoter region methylation supports a pathogenetic role in breast and ovarian cancer. Carcinogenesis 21: 147-151.

Boyer JC, Risinger JI, Farber RA. 1998. Stability of microsatellites in myeloid neoplasias. Cancer Genet Cytogenet 106: 54-61.

Calasanz MJ, Cigudosa JC, Odero MD, Ferreira C, Ardanaz MT, Fraile A, Carrasco JL, Sole F, Cuesta B, Gullon A. 1997. Cytogenetic analysis of 280 patients with multiple myeloma and related disorders: primary breakpoints and clinical correlations. Genes Chromosomes Cancer 18: 84-93.

Champlin RE, Golde DW. 1985. Chronic myelogenous leukemia: recent advances. Blood 65: 1039-1047.

Choudhury A, Elliott F, Iles MM, Churchman M, Bristow RG, Bishop DT, Kiltie AE. 2008. Analysis of variants in DNA damage signalling genes in bladder cancer. BMC Med Genet 9: 69.

Christodoulopoulos G, Malapetsa A, Schipper H, Golub E, Radding C, Panasci LC. 1999. Chlorambucil induction of HsRad51 in B-cell chronic lymphocytic leukemia. Clin Cancer Res 5: 2178-2184.

Cibeira MT, Fernandez de Larrea C, Navarro A, Diaz T, Fuster D, Tovar N, Rosinol L, Monzo M, Blade J. 2011. Impact on response and survival of DNA repair single nucleotide polymorphisms in relapsed or refractory multiple myeloma patients treated with thalidomide. Leuk Res.

Cline SD, Hanawalt PC. 2003. Who's on first in the cellular response to DNA damage? Nat Rev Mol Cell Biol 4: 361-372.

da Silva Silveira V, Canalle R, Scrideli CA, Queiroz RG, Bettiol H, Valera ET, Tone LG. 2009. Polymorphisms of xenobiotic metabolizing enzymes and DNA repair genes and outcome in childhood acute lymphoblastic leukemia. Leuk Res 33: 898-901.

de Laat WL, Jaspers NG, Hoeijmakers JH. 1999. Molecular mechanism of nucleotide excision repair. Genes Dev 13: 768-785.

den Dunnen JT, Antonarakis SE. 2000. Mutation nomenclature extensions and suggestions to describe complex mutations: a discussion. Hum Mutat 15: 7-12.

—. 2003. Mutation nomenclature. Curr Protoc Hum Genet Chapter 7: Unit 7 13.

Deutsch E, et al. 2001. BCR-ABL down-regulates the DNA repair protein DNA-PKcs. Blood 97: 2084-2090.

Doll DC, List AF. 1989. Myelodysplastic syndromes. West J Med 151: 161-167.

Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. 1996. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 2: 561-566.

Economopoulou P, et al. 2009. Expression analysis of proteins involved in the non homologous end joining DNA repair mechanism, in the bone marrow of adult de novo myelodysplastic syndromes. Ann Hematol.

El-Zein R, Monroy CM, Etzel CJ, Cortes AC, Xing Y, Collier AL, Strom SS. 2009. Genetic polymorphisms in DNA repair genes as modulators of Hodgkin disease risk. Cancer 115: 1651-1659.

Elliott SL, et al. 2011. Mitoxantrone in combination with an inhibitor of DNA-dependent protein kinase: a potential therapy for high risk B-cell chronic lymphocytic leukaemia. Br J Haematol 152: 61-71.

Enjuanes A, et al. 2008. Genetic variants in apoptosis and immunoregulation-related genes are associated with risk of chronic lymphocytic leukemia. Cancer Res 68: 10178-10186.

Esteller M, Corn PG, Baylin SB, Herman JG. 2001. A gene hypermethylation profile of human cancer. Cancer Res 61: 3225-3229.

Fabiani E, et al. 2009. Polymorphisms of detoxification and DNA repair enzymes in myelodyplastic syndromes. Leuk Res 33: 1068-1071.

Faderl S, Kantarjian HM, Talpaz M, Estrov Z. 1998. Clinical significance of cytogenetic abnormalities in adult acute lymphoblastic leukemia. Blood 91: 3995-4019.

Fang NY, et al. 2003. Oligonucleotide microarrays demonstrate the highest frequency of ATM mutations in the mantle cell subtype of lymphoma. Proc Natl Acad Sci U S A 100: 5372-5377.

Fenton JA, Pratt G, Rawstron AC, Morgan GJ. 2002. Isotype class switching and the pathogenesis of multiple myeloma. Hematol Oncol 20: 75-85.

Fonseca R, et al. 2004. Genetics and cytogenetics of multiple myeloma: a workshop report. Cancer Res 64: 1546-1558.

Fortini P, Dogliotti E. 2007. Base damage and single-strand break repair: mechanisms and functional significance of short- and long-patch repair subpathways. DNA Repair (Amst) 6: 398-409.

Fortini P, Parlanti E, Sidorkina OM, Laval J, Dogliotti E. 1999. The type of DNA glycosylase determines the base excision repair pathway in mammalian cells. J Biol Chem 274: 15230-15236.

Friedenson B. 2007. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer 7: 152.

Ganster C, Neesen J, Zehetmayer S, Jager U, Esterbauer H, Mannhalter C, Kluge B, Fonatsch C. 2009. DNA repair polymorphisms associated with cytogenetic subgroups in B-cell chronic lymphocytic leukemia. Genes Chromosomes Cancer 48: 760-767.

Gillert E, et al. 1999. A DNA damage repair mechanism is involved in the origin of chromosomal translocations t(4;11) in primary leukemic cells. Oncogene 18: 4663-4671.

Gillet LC, Scharer OD. 2006. Molecular mechanisms of mammalian global genome nucleotide excision repair. Chem Rev 106: 253-276.

Gu L, Cline-Brown B, Zhang F, Qiu L, Li GM. 2002. Mismatch repair deficiency in hematological malignancies with microsatellite instability. Oncogene 21: 5758-5764.

Hakem R. 2008. DNA-damage repair; the good, the bad, and the ugly. Embo J 27: 589-605.

Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. 1999. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 94: 1848-1854.

Hangaishi A, Ogawa S, Mitani K, Hosoya N, Chiba S, Yazaki Y, Hirai H. 1997. Mutations and loss of expression of a mismatch repair gene, hMLH1, in leukemia and lymphoma cell lines. Blood 89: 1740-1747.

Hayden PJ, et al. 2007. Variation in DNA repair genes XRCC3, XRCC4, XRCC5 and susceptibility to myeloma. Hum Mol Genet 16: 3117-3127.

Helleday T, Lo J, van Gent DC, Engelward BP. 2007. DNA double-strand break repair: from mechanistic understanding to cancer treatment. DNA Repair (Amst) 6: 923-935.

Hill DA, et al. 2006. Risk of non-Hodgkin lymphoma (NHL) in relation to germline variation in DNA repair and related genes. Blood 108: 3161-3167.

Ho PJ, Brown RD, Pelka GJ, Basten A, Gibson J, Joshua DE. 2001. Illegitimate switch recombinations are present in approximately half of primary myeloma tumors, but do not relate to known prognostic indicators or survival. Blood 97: 490-495.

Hwang BJ, Ford JM, Hanawalt PC, Chu G. 1999. Expression of the p48 xeroderma pigmentosum gene is p53-dependent and is involved in global genomic repair. Proc Natl Acad Sci U S A 96: 424-428.

Infante-Rivard C, Mathonnet G, Sinnett D. 2000. Risk of childhood leukemia associated with diagnostic irradiation and polymorphisms in DNA repair genes. Environ Health Perspect 108: 495-498.

Inokuchi K, Ikejima M, Watanabe A, Nakajima E, Orimo H, Nomura T, Shimada T. 1995. Loss of expression of the human MSH3 gene in hematological malignancies. Biochem Biophys Res Commun 214: 171-179.

Janssen JW, et al. 1989. Clonal analysis of myelodysplastic syndromes: evidence of multipotent stem cell origin. Blood 73: 248-254.

Jiang L, Liang J, Jiang M, Yu X, Zheng J, Liu H, Wu D, Zhou Y. 2011. Functional polymorphisms in the NBS1 gene and acute lymphoblastic leukemia susceptibility in a Chinese population. Eur J Haematol 86: 199-205.

Jiricny J. 1998. Replication errors: cha(lle)nging the genome. Embo J 17: 6427-6436.

—. 2006. The multifaceted mismatch-repair system. Nat Rev Mol Cell Biol 7: 335-346.

Johnson N, et al. 2007. Counting potentially functional variants in BRCA1, BRCA2 and ATM predicts breast cancer susceptibility. Hum Mol Genet 16: 1051-1057.

Joseph T, Kusumakumary P, Chacko P, Abraham A, Pillai MR. 2005. DNA repair gene XRCC1 polymorphisms in childhood acute lymphoblastic leukemia. Cancer Lett 217: 17-24.

Kanaar R, Wyman C, Rothstein R. 2008. Quality control of DNA break metabolism: in the 'end', it's a good thing. Embo J 27: 581-588.

Kaneko H, Horiike S, Inazawa J, Nakai H, Misawa S. 1995. Microsatellite instability is an early genetic event in myelodysplastic syndrome. Blood 86: 1236-1237.

Karagiannis TC, El-Osta A. 2004. Double-strand breaks: signaling pathways and repair mechanisms. Cell Mol Life Sci 61: 2137-2147.

Kim JE, Minter-Dykhouse K, Chen J. 2006. Signaling networks controlled by the MRN complex and MDC1 during early DNA damage responses. Mol Carcinog 45: 403-408.

Kotoula V, Hytiroglou P, Kaloutsi V, Barbanis S, Kouidou S, Papadimitriou CS. 2002. Mismatch repair gene expression in malignant lymphoproliferative disorders of B-cell origin. Leuk Lymphoma 43: 393-399.

Kuptsova N, Kopecky KJ, Godwin J, Anderson J, Hoque A, Willman CL, Slovak ML, Ambrosone CB. 2007. Polymorphisms in DNA repair genes and therapeutic outcomes of AML patients from SWOG clinical trials. Blood 109: 3936-3944.

Kyle RA, Rajkumar SV. 2004. Multiple myeloma. N Engl J Med 351: 1860-1873.

Li L, Yang L, Zhang Y, Xu Z, Qin T, Hao Y, Xiao Z. 2010. Detoxification and DNA repair genes polymorphisms and susceptibility of primary myelodysplastic syndromes in Chinese population. Leuk Res.

Liberzon E, Avigad S, Yaniv I, Stark B, Avrahami G, Goshen Y, Zaizov R. 2004. Molecular variants of the ATM gene in Hodgkin's disease in children. Br J Cancer 90: 522-525.

Lieberman HB. 2008. DNA damage repair and response proteins as targets for cancer therapy. Curr Med Chem 15: 360-367.

Liebisch P, Dohner H. 2006. Cytogenetics and molecular cytogenetics in multiple myeloma. Eur J Cancer 42: 1520-1529.

Liu A, Takakuwa T, Fujita S, Luo WJ, Tresnasari K, Van den Berg A, Poppema S, Aozasa K. 2008. ATR alterations in Hodgkin's lymphoma. Oncol Rep 19: 999-1005.

Liu J, Song B, Wang Z, Song X, Shi Y, Zheng J, Han J. 2009. DNA repair gene XRCC1 polymorphisms and non-Hodgkin lymphoma risk in a Chinese population. Cancer Genet Cytogenet 191: 67-72.

Liu L, Yang L, Mi Y, Wang J, Li J, Zhang Y, Ma X, Qin T, Xu Z, Xiao Z. 2011. RAD51 and XRCC3 polymorphisms: Impact on the risk and treatment outcomes of de novo inv(16) or t(16;16)/CBFbeta-MYH11(+) acute myeloid leukemia. Leuk Res.

Lockett KL, Snowhite IV, Hu JJ. 2005. Nucleotide-excision repair and prostate cancer risk. Cancer Lett 220: 125-135.

M'Kacher R, et al. 2007. Telomere shortening and associated chromosomal instability in peripheral blood lymphocytes of patients with Hodgkin's lymphoma prior to any treatment are predictive of second cancers. Int J Radiat Oncol Biol Phys 68: 465-471.

Madhusudan S, Middleton MR. 2005. The emerging role of DNA repair proteins as predictive, prognostic and therapeutic targets in cancer. Cancer Treat Rev 31: 603-617.

Mao G, Yuan F, Absher K, Jennings CD, Howard DS, Jordan CT, Gu L. 2008. Preferential loss of mismatch repair function in refractory and relapsed acute myeloid leukemia: potential contribution to AML progression. Cell Res 18: 281-289.

Martin P, Santon A, Garcia-Cosio M, Bellas C. 2006. hMLH1 and MGMT inactivation as a mechanism of tumorigenesis in monoclonal gammopathies. Mod Pathol 19: 914-921.

Mathonnet G, Krajinovic M, Labuda D, Sinnett D. 2003. Role of DNA mismatch repair genetic polymorphisms in the risk of childhood acute lymphoblastic leukaemia. Br J Haematol 123: 45-48.

Meza-Espinoza JP, Peralta-Leal V, Gutierrez-Angulo M, Macias-Gomez N, Ayala-Madrigal ML, Barros-Nunez P, Duran-Gonzalez J, Leal-Ugarte E. 2009. XRCC1 polymorphisms and haplotypes in Mexican patients with acute lymphoblastic leukemia. Genet Mol Res 8: 1451-1458.

Molenaar JJ, Gerard B, Chambon-Pautas C, Cave H, Duval M, Vilmer E, Grandchamp B. 1998. Microsatellite instability and frameshift mutations in BAX and transforming growth factor-beta RII genes are very uncommon in acute lymphoblastic leukemia in vivo but not in cell lines. Blood 92: 230-233.

Monroy CM, Cortes AC, Lopez M, Rourke E, Etzel CJ, Younes A, Strom SS, El-Zein R. 2011. Hodgkin lymphoma risk: Role of genetic polymorphisms and gene-gene interactions in DNA repair pathways. Mol Carcinog.

Monzo M, et al. 2006. Genomic polymorphisms provide prognostic information in intermediate-risk acute myeloblastic leukemia. Blood 107: 4871-4879.

Morimoto H, Tsukada J, Kominato Y, Tanaka Y. 2005. Reduced expression of human mismatch repair genes in adult T-cell leukemia. Am J Hematol 78: 100-107.

Noel P, Solberg LA, Jr. 1992. Myelodysplastic syndromes. Pathogenesis, diagnosis and treatment. Crit Rev Oncol Hematol 12: 193-215.

Nowicki MO, Falinski R, Koptyra M, Slupianek A, Stoklosa T, Gloc E, Nieborowska-Skorska M, Blasiak J, Skorski T. 2004. BCR/ABL oncogenic kinase promotes unfaithful repair of the reactive oxygen species-dependent DNA double-strand breaks. Blood 104: 3746-3753.

Oehler VG, et al. 2007. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 109: 1782-1789.

Ogino S, Gulley ML, den Dunnen JT, Wilson RB. 2007. Standard mutation nomenclature in molecular diagnostics: practical and educational challenges. J Mol Diagn 9: 1-6.

Olive PL. 1998. The role of DNA single- and double-strand breaks in cell killing by ionizing radiation. Radiat Res 150: S42-51.

Pakakasama S, Sirirat T, Kanchanachumpol S, Udomsubpayakul U, Mahasirimongkol S, Kitpoka P, Thithapandha A, Hongeng S. 2007. Genetic polymorphisms and haplotypes of DNA repair genes in childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 48: 16-20.

Palitti F. 2004. Mechanisms of formation of chromosomal aberrations: insights from studies with DNA repair-deficient cells. Cytogenet Genome Res 104: 95-99.

Park CJ, Choi BS. 2006. The protein shuffle. Sequential interactions among components of the human nucleotide excision repair pathway. Febs J 273: 1600-1608.

Peng B, Hodge DR, Thomas SB, Cherry JM, Munroe DJ, Pompeia C, Xiao W, Farrar WL. 2005. Epigenetic silencing of the human nucleotide excision repair gene, hHR23B, in interleukin-6-responsive multiple myeloma KAS-6/1 cells. J Biol Chem 280: 4182-4187.

Rajkumar S, Fonseca R, Lacy M, Witzig T, Lust J, Greipp P, Therneau T, Kyle R, Litzow M, Gertz M. 1999. Abnormal cytogenetics predict poor survival after high-dose therapy and autologous blood cell transplantation in multiple myeloma. Bone Marrow Transplant 24: 497-503.

Roddam PL, Rollinson S, O'Driscoll M, Jeggo PA, Jack A, Morgan GJ. 2002. Genetic variants of NHEJ DNA ligase IV can affect the risk of developing multiple myeloma, a tumour characterised by aberrant class switch recombination. J Med Genet 39: 900-905.

Roddam PL, Allan JM, Dring AM, Worrillow LJ, Davies FE, Morgan GJ. 2010. Non-homologous end-joining gene profiling reveals distinct expression patterns associated with lymphoma and multiple myeloma. Br J Haematol 149: 258-262.

Rollinson S, Kesby H, Morgan GJ. 2006. Haplotypic variation in MRE11, RAD50 and NBS1 and risk of non-Hodgkin's lymphoma. Leuk Lymphoma 47: 2567-2583.

Rollinson S, Smith AG, Allan JM, Adamson PJ, Scott K, Skibola CF, Smith MT, Morgan GJ. 2007. RAD51 homologous recombination repair gene haplotypes and risk of acute myeloid leukaemia. Leuk Res 31: 169-174.

Rowley JD. 1999. The role of chromosome translocations in leukemogenesis. Semin Hematol 36: 59-72.

Salles D, Mencalha AL, Ireno IC, Wiesmuller L, Abdelhay E. 2011. BCR-ABL stimulates mutagenic homologous DNA double-strand break repair via the DNA-end-processing factor CtIP. Carcinogenesis 32: 27-34.

Sampath D, Plunkett W. 2007. The role of DNA repair in chronic lymphocytic leukemia pathogenesis and chemotherapy resistance. Curr Oncol Rep 9: 361-367.

Sancar A. 1996. DNA excision repair. Annu Rev Biochem 65: 43-81.

Scardocci A, et al. 2006. Reduced BRCA1 expression due to promoter hypermethylation in therapy-related acute myeloid leukaemia. Br J Cancer 95: 1108-1113.

Schaffner C, Idler I, Stilgenbauer S, Dohner H, Lichter P. 2000. Mantle cell lymphoma is characterized by inactivation of the ATM gene. Proc Natl Acad Sci U S A 97: 2773-2778.

Scharer OD. 2003. Chemistry and biology of DNA repair. Angew Chem Int Ed Engl 42: 2946-2974.

Schuetz JM, MaCarthur AC, Leach S, Lai AS, Gallagher RP, Connors JM, Gascoyne RD, Spinelli JJ, Brooks-Wilson AR. 2009. Genetic variation in the NBS1, MRE11, RAD50 and BLM genes and susceptibility to non-Hodgkin lymphoma. BMC Med Genet 10: 117.

Schwartz CL, Cohen HJ. 1988. Preleukemic syndromes and other syndromes predisposing to leukemia. Pediatr Clin North Am 35: 853-871.

Seedhouse C, Faulkner R, Ashraf N, Das-Gupta E, Russell N. 2004. Polymorphisms in genes involved in homologous recombination repair interact to increase the risk of developing acute myeloid leukemia. Clin Cancer Res 10: 2675-2680.

Sellick GS, Wade R, Richards S, Oscier DG, Catovsky D, Houlston RS. 2008. Scan of 977 nonsynonymous SNPs in CLL4 trial patients for the identification of genetic variants influencing prognosis. Blood 111: 1625-1633.

Seviour EG, Lin SY. 2010. The DNA damage response: Balancing the scale between cancer and ageing. Aging (Albany NY) 2: 900-907.

Shammas MA, Shmookler Reis RJ, Koley H, Batchu RB, Li C, Munshi NC. 2009. Dysfunctional homologous recombination mediates genomic instability and progression in myeloma. Blood 113: 2290-2297.

Shen M, et al. 2007. Polymorphisms in DNA repair genes and risk of non-Hodgkin's lymphoma in New South Wales, Australia. Haematologica 92: 1180-1185.

—. 2006. Polymorphisms in DNA repair genes and risk of non-Hodgkin lymphoma among women in Connecticut. Hum Genet 119: 659-668.

—. 2010. Polymorphisms in DNA repair genes and risk of non-Hodgkin lymphoma in a pooled analysis of three studies. Br J Haematol 151: 239-244.

Shi JY, Ren ZH, Jiao B, Xiao R, Yun HY, Chen B, Zhao WL, Zhu Q, Chen Z, Chen SJ. 2011. Genetic variations of DNA repair genes and their prognostic significance in patients with acute myeloid leukemia. Int J Cancer 128: 233-238.

Sill H, Goldman JM, Cross NC. 1996. Rarity of microsatellite alterations in acute myeloid leukaemia. Br J Cancer 74: 255-257.

Sipahimalani P, et al. 2007. A systematic evaluation of the ataxia telangiectasia mutated gene does not show an association with non-Hodgkin lymphoma. Int J Cancer 121: 1967-1975.

Slupianek A, Poplawski T, Jozwiakowski SK, Cramer K, Pytel D, Stoczynska E, Nowicki MO, Blasiak J, Skorski T. 2011. BCR/ABL stimulates WRN to promote survival and genomic instability. Cancer Res 71: 842-851.

Smadja NV, Bastard C, Brigaudeau C, Leroux D, Fruchart C. 2001. Hypodiploidy is a major prognostic factor in multiple myeloma. Blood 98: 2229-2238.

Smedby KE, et al. 2006. Variation in DNA repair genes ERCC2, XRCC1, and XRCC3 and risk of follicular lymphoma. Cancer Epidemiol Biomarkers Prev 15: 258-265.

Stanczyk M, Sliwinski T, Cuchra M, Zubowska M, Bielecka-Kowalska A, Kowalski M, Szemraj J, Mlynarski W, Majsterek I. 2011. The association of polymorphisms in

DNA base excision repair genes XRCC1, OGG1 and MUTYH with the risk of childhood acute lymphoblastic leukemia. Mol Biol Rep 38: 445-451.

Stenson PD, Mort M, Ball EV, Howells K, Phillips AD, Thomas NS, Cooper DN. 2009. The Human Gene Mutation Database: 2008 update. Genome Med 1: 13.

Strom SS, Estey E, Outschoorn UM, Garcia-Manero G. 2010. Acute myeloid leukemia outcome: role of nucleotide excision repair polymorphisms in intermediate risk patients. Leuk Lymphoma 51: 598-605.

Tai YT, Podar K, Kraeft SK, Wang F, Young G, Lin B, Gupta D, Chen LB, Anderson KC. 2002. Translocation of Ku86/Ku70 to the multiple myeloma cell membrane: functional implications. Exp Hematol 30: 212-220.

Takagi M, et al. 2004. Identification and characterization of polymorphic variations of the ataxia telangiectasia mutated (ATM) gene in childhood Hodgkin disease. Blood 103: 283-290.

Takeda N, Shibuya M, Maru Y. 1999. The BCR-ABL oncoprotein potentially interacts with the xeroderma pigmentosum group B protein. Proc Natl Acad Sci U S A 96: 203-207.

Takeuchi S, et al. 1997. Microsatellite instability and other molecular abnormalities in childhood acute lymphoblastic leukaemia. Br J Haematol 98: 134-139.

Tasak T, Lee S, Spira S, Takeuchi S, Hatta Y, Nagai M, Takahara J, Koeffler HP. 1996. Infrequent microsatellite instability during the evolution of myelodysplastic syndrome to acute myelocytic leukemia. Leuk Res 20: 113-117.

Taylor AM, Metcalfe JA, Thick J, Mak YF. 1996. Leukemia and lymphoma in ataxia telangiectasia. Blood 87: 423-438.

Timuragaoglu A, Demircin S, Dizlek S, Alanoglu G, Kiris E. 2009. Microsatellite instability is a common finding in multiple myeloma. Clin Lymphoma Myeloma 9: 371-374.

Tumer TB, Yilmaz D, Tanrikut C, Sahin G, Ulusoy G, Arinc E. 2010. DNA repair XRCC1 Arg399Gln polymorphism alone, and in combination with CYP2E1 polymorphisms significantly contribute to the risk of development of childhood acute lymphoblastic leukemia. Leuk Res 34: 1275-1281.

Vangsted A, Gimsing P, Klausen TW, Nexo BA, Wallin H, Andersen P, Hokland P, Lillevang ST, Vogel U. 2007. Polymorphisms in the genes ERCC2, XRCC3 and CD3EAP influence treatment outcome in multiple myeloma patients undergoing autologous bone marrow transplantation. Int J Cancer 120: 1036-1045.

Velangi MR, Matheson EC, Morgan GJ, Jackson GH, Taylor PR, Hall AG, Irving JA. 2004. DNA mismatch repair pathway defects in the pathogenesis and evolution of myeloma. Carcinogenesis 25: 1795-1803.

Vogel U, Olsen A, Wallin H, Overvad K, Tjonneland A, Nexo BA. 2005. Effect of polymorphisms in XPD, RAI, ASE-1 and ERCC1 on the risk of basal cell carcinoma among Caucasians after age 50. Cancer Detect Prev 29: 209-214.

Vorechovsky I, Luo L, Dyer MJ, Catovsky D, Amlot PL, Yaxley JC, Foroni L, Hammarstrom L, Webster AD, Yuille MA. 1997. Clustering of missense mutations in the ataxia-telangiectasia gene in a sporadic T-cell leukaemia. Nat Genet 17: 96-99.

Voso MT, Fabiani E, D'Alo F, Guidi F, Di Ruscio A, Sica S, Pagano L, Greco M, Hohaus S, Leone G. 2007. Increased risk of acute myeloid leukaemia due to polymorphisms in detoxification and DNA repair enzymes. Ann Oncol 18: 1523-1528.

Wagner JE, et al. 2004. Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. Blood 103: 3226-3229.

Wang SL, Zhao H, Zhou B, Chen YL, Zou Y, Zhu XF, Li QS, Han MZ, Yang RC, Han ZC. 2006. Polymorphisms in ERCC1 and susceptibility to childhood acute lymphoblastic leukemia in a Chinese population. Leuk Res 30: 1341-1345.

Wheeler DL, et al. 2007. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res 35: D5-12.

Wiemels JL, Alexander FE, Cazzaniga G, Biondi A, Mayer SP, Greaves M. 2000. Microclustering of TEL-AML1 translocation breakpoints in childhood acute lymphoblastic leukemia. Genes Chromosomes Cancer 29: 219-228.

Wiemels JL, et al. 2002. In utero origin of t(8;21) AML1-ETO translocations in childhood acute myeloid leukemia. Blood 99: 3801-3805.

Willmore E, et al. 2008. DNA-dependent protein kinase is a therapeutic target and an indicator of poor prognosis in B-cell chronic lymphocytic leukemia. Clin Cancer Res 14: 3984-3992.

Wood RD. 1997. Nucleotide excision repair in mammalian cells. J Biol Chem 272: 23465-23468.

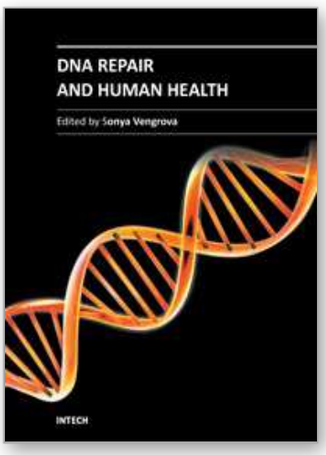
Worrillow L, Roman E, Adamson PJ, Kane E, Allan JM, Lightfoot TJ. 2009. Polymorphisms in the nucleotide excision repair gene ERCC2/XPD and risk of non-Hodgkin lymphoma. Cancer Epidemiol 33: 257-260.

Xu ZY, Loignon M, Han FY, Panasci L, Aloyz R. 2005. Xrcc3 induces cisplatin resistance by stimulation of Rad51-related recombinational repair, S-phase checkpoint activation, and reduced apoptosis. J Pharmacol Exp Ther 314: 495-505.

Yang C, Betti C, Singh S, Toor A, Vaughan A. 2009. Impaired NHEJ function in multiple myeloma. Mutat Res 660: 66-73.

Yoshida H, Naoe T, Fukutani H, Kiyoi H, Kubo K, Ohno R. 1995. Analysis of the joining sequences of the t(15;17) translocation in human acute promyelocytic leukemia: sequence non-specific recombination between the PML and RARA genes within identical short stretches. Genes Chromosomes Cancer 12: 37-44.

Zhu R, Lu FJ, Zhang ZB, Zhai XW, Liu J, Lu G, Wu Y, Chen C, Xia Z. 2005. [Association of genetic polymorphism of XRCC1 with susceptibility to acute childhood leukemia]. Wei Sheng Yan Jiu 34: 300-302.



DNA Repair and Human Health

Edited by Dr. Sonya Vengrova

ISBN 978-953-307-612-6
Hard cover, 792 pages
Publisher InTech
Published online 26, October, 2011
Published in print edition October, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Panagiota Economopoulou, Vassiliki Pappa, Sotirios Papageorgiou, John Dervenoulas and Theofanis Economopoulos (2011). DNA Repair Deficiency Associated with Hematological Neoplasms, DNA Repair and Human Health, Dr. Sonya Vengrova (Ed.), ISBN: 978-953-307-612-6, InTech, Available from: http://www.intechopen.com/books/dna-repair-and-human-health/dna-repair-deficiency-associated-with-hematological-neoplasms

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen