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REVIEW

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Involvement of classic and alternative non-homologous end joining pathways in hematologic malignancies: targeting strategies for treatment

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Abstract

Chromosomal translocations are the main etiological factor of hematologic malignancies. These translocations are generally the consequence of aberrant DNA double-strand break (DSB) repair. DSBs arise either exogenously or endogenously in cells and are repaired by major pathways, including non-homologous end-joining (NHEJ), homologous recombination (HR), and other minor pathways such as alternative end-joining (A-EJ). Therefore, defective NHEJ, HR, or A-EJ pathways force hematopoietic cells toward tumorigenesis. As some components of these repair pathways are overactivated in various tumor entities, targeting these pathways in cancer cells can sensitize them, especially resistant clones, to radiation or chemotherapy agents. However, targeted therapy-based studies are currently underway in this area, and furtherly there are some biological pitfalls, clinical issues, and limitations related to these targeted therapies, which need to be considered. This review aimed to investigate the alteration of DNA repair elements of C-NHEJ and A-EJ in hematologic malignancies and evaluate the potential targeted therapies against these pathways.

Keywords: Double-strand break, Double-strand break repair, Non-homologous end-joining, Alternative end-joining pathways, Hematologic malignancies, Targeted therapy

Introduction

There are different types of DNA damage including Bulky adducts/intrastrand crosslinks, single-strand break, DNA double-strand break (DSB), and base mismatch (Fig. 1). DSBs are the most destructive genomic damages [1, 2], that may arise either exogenously or endogenously. While the exogenous sources of DSBs include ionizing radiation and DNA damaging agents (clastogens), the endogenous sources commonly result from damages during replication, which, if unrepaired, can stimulate genomic instability [3, 4]. Some mechanisms involved in endogenous DSB formation include V(D)J recombination in progenitors of lymphocytes, class-switch recombination (CSR) in lymphocytes, and meiosis followed by gametogenesis [5].

On the other hand, DSB genotoxicity can be compensated by two major pathways: (1) homologous recombination (HR); and (2) non-homologous end-joining (NHEJ), including classical non-homologous end-joining (C-NHEJ) and alternative non-homologous end-joining (A-NHEJ or A-EJ) pathways [5]. The NHEJ pathways rejoin two broken DNA ends and repair DSBs in G1 or G0 phase of the cell cycle. While recognition of DNA ends by C-NHEJ pathways is dependent on XRCC5, XRCC6, DNA-PKcs, and ligation by DNA ligase IV (Lig IV)/XRCC4, the A-EJ pathways are independent of Lig IV and can recognize DNA ends by a diverse set of factors, including different DNA polymerases (δ and θ),

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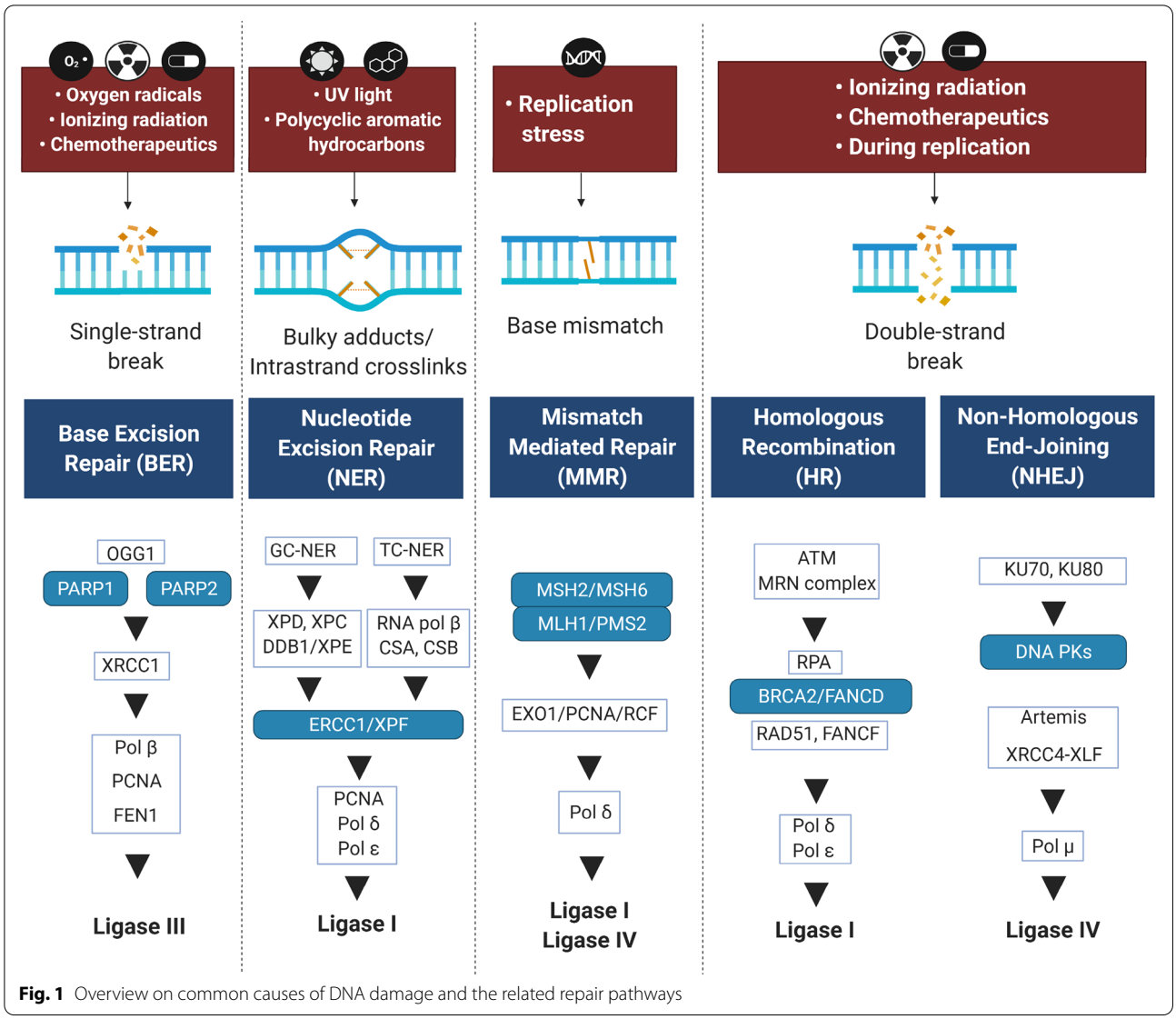

Fig. 1 Overview on common causes of DNA damage and the related repair pathways

DNA nucleases (ERCC1-XPF), and ligases (Lig I and Lig III/XRCC1) [6].

Aberrant repair of DSBs can result in miss-joining of DNA repair components with DNA ends and cause deletions, inversions, or complex rearrangements of chromosomes. These changes all lead to genomic instability, tumor susceptibility, immunodeficiency, and a wide range of human cancers, including hematologic malignancies [6–8]. Genomic instability due to the aberrant activity of NHEJ pathways can also increase the ratio of acquired mutations or translocations, including recurrent translocations in hematologic malignancies, such as BCR-ABL and MLL translocations, as the most important ones [9–11].

Several studies have shown that chemo- or radio-resistant leukemic cells have altered levels of C-NHEJ and A-EJ activities, compared to their sensitive counterparts. Considering the development and progression of hematologic malignancies via DNA damage and repair response abnormalities, it seems that use of DSB inducers, in combination with DSB repair (DSBR) inhibitors, may be a promising strategy to eradicate malignant cells and provide a novel therapeutic approach. Therefore, this study aimed to investigate the role of C-NHEJ and A-EJ pathways in the progression of hematologic malignancies and to evaluate targeting of these pathways for reducing the mortality of patients.

Mechanisms of C-NHEJ and A-EJ pathways in DSBR

In human cells, C-NHEJ is a rapid, high-capacity pathway that mediates the direct religation of the broken DNA molecule with minimal reference to the DNA

sequence. In contrast to HR, C-NHEJ does not require an extensive homologous template; therefore, it is more error-prone and theoretically is not restricted to a certain cell cycle phase [12]. The mechanism of C-NHEJ can be broken down into several sequential steps. The initial step is the recognition and binding of the Ku70–Ku80 (also known as XRCC6–XRCC5) heterodimer to the DSB. Ku heterodimer serves as a 'tool belt' or a scaffold that directly or indirectly recruits other NHEJ proteins [13]. As an essential event, Ku70/80 directly recruits DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to the DNA ends. DNA-PKcs has a strong affinity for Ku–DNA ends and, together with Ku, form the DNA-PK complex. Following the binding of DNA-PKcs to the DNA-Ku complex, the Ku heterodimer translocates inward on the dsDNA strand and eventually results in serine/threonine protein kinase activation of the DNA-PKcs [14]. DNA-PKcs undergoes autophosphorylation and activates Artemis, the main nuclease in NHEJ, which then gains the ability to trim overhangs to expose complementary regions. The trimming of different end structures such as DNA loops, flaps, or gaps by Artemis makes them suitable for the ligation of the XRCC4–LIG IV complex (Fig. 2) [13, 15].

For more complex ends, other factors (e.g., PNKP, APTX, APLF, and PALF) and polymerases (pol μ and pol λ) are required [16, 17]. To ligate the broken ends, the Ku-DNA complex anchors PAXX, XRCC4, XLF

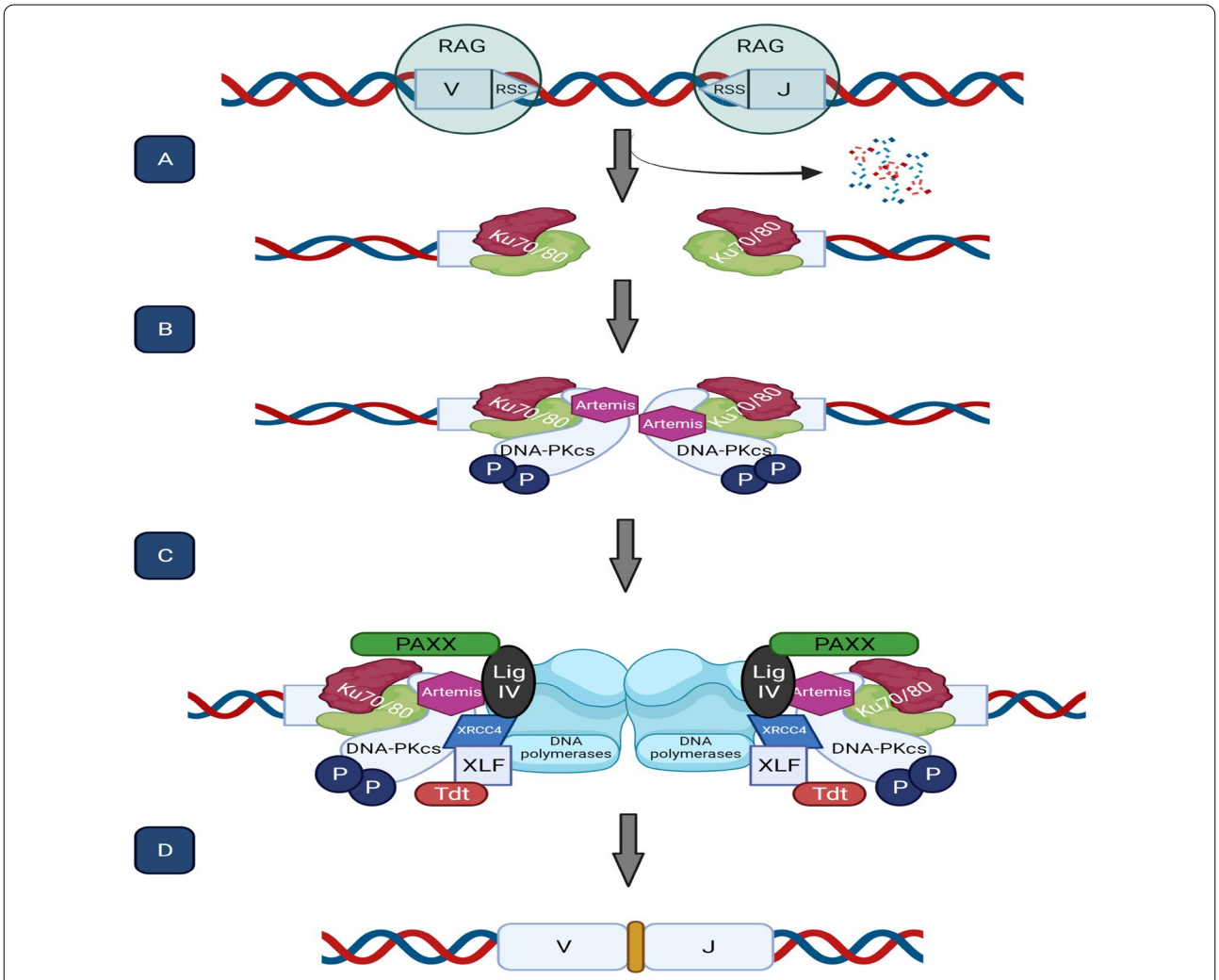

Fig. 2 C-NHEJ in V(D)J recombination process. **A** RAG proteins bind to the V(D)J sequence at DNA, leading to DNA cleavage, creating DSB. Afterward, Ku70/80 heterodimers locate and bind to the DSB end. **B** Ku70/80 directly recruits DNA-PKcs. Following DNA-PKcs autophosphorylation, it activates the main nuclease in c-NHEJ, Artemis. **C** After trimming of DNA ends by Artemis, DNA polymerases reconstruct the DNA. Consequently, the Ku-DNA complex anchors PAXX, XRCC4, XLF, and Lig IV to rejoin the DNA ends. D Fully functional recombined DNA is ready to be translated

(NHEJ1 or Cernunnos), and Lig IV, rejoining the DNA ends [18].

A-EJ components and mechanisms

In mammalian cells, the repair of DSBs by A-EJ is more evident in the absence of a functional C-NHEJ pathway [19, 20]. There is an increasing interest in A-EJ pathways in malignant cells, as they create large deletions, translocations, and genomic rearrangements [21–23]. Therefore, they might serve as promising therapeutic targets in tumor cells with deficiencies in main DSB repair pathways. These pathways are Ku-independent and require DNA end resection, similar to HR. Since the broken ends can be rejoined without using a homologous template, this process also shares similarities with NHEJ [24]. Based on the amount of DNA sequence homology used to align DNA ends, the A-EJ mechanisms are mediated by two minor pathways: single-strand annealing (SSA) and microhomology-mediated end-joining (MMEJ) [25]. While SSA comprises complementary repeat sequences greater than 25 nucleotides, MMEJ involves microhomologies which are shorter tracts of sequence homology (2–20 nucleotides) [26].

Several studies have shown that PARP1 binds to single-strand DNA and is essential for the initial phase of A-EJ (recognition and tethering). First, it catalyzes the poly-ADP-ribosylation of proteins at DNA damage sites [27]. Next, it contributes to the initial assembling of the MRN complex (including MRE11, RAD50, and NBS1) on DSBs, leading to the activation of ataxia telangiectasia mutated (ATM) and RAD3-related (ATR) kinases [28]. This complex causes DNA end resection, which involves two major steps. In the first step, the combination of MRN and C-terminal interacting protein (CtIP) creates short single-stranded DNA (ssDNA), and then exonuclease 1 (EXO1) or Bloom's helicase (BLM)/DNA2 endonuclease complex causes an extensive end resection [29]. EXO1 is loaded on ssDNA by Metnase (or SETMAR), a chimeric fusion protein consisting of a transposase domain and a histone methylase domain; the former is MAR, and the latter is called SET [30]. Metnase enhances DSBR through the C-NHEJ pathway by interacting with DNA Lig IV [31]. Also, Metnase and Artemis nucleases determine the fidelity of end-joining repair in mammalian cells (Fig. 2) [32].

The second step of DNA end resection is dispensable for MMEJ [26]. Polymerases, flap endonucleases, helicases, and polynucleotide kinases prepare the DNA ends for ligation [5]. Pol θ fills the gap in MMEJ, whereas the gap-filling component of SSA is unidentified [26]. Finally, Lig III ligates the DNA ends, although other components, such as XRCC1, as a scaffolding protein, are needed [33]. It should be noted that interlinking issues are one of the important factors in the repair process and selection of a pathway, as well as targeted therapy. Overall, neddylation, ubiquitination, and interference of non-coding RNAs are the most common interlinking issues in DSBR [34–36]. Moreover, the mechanism of the A-EJ pathway is shown in Fig. 3.

C-NHEJ and A-EJ alterations in hematologic malignancies

Hematologic malignancies have been at the forefront of cancers in terms of using genetic analyses for diagnosis, classification, prognosis, and clinical therapeutic management of patients. Genomic analysis has dramatically influenced the clinical evaluation of nearly every form of hematologic malignancy. DNA repair has a critical role in protecting cells against endogenous or exogenous insults that can cause varying degrees of DNA damage. Any deficiency in DNA repair pathways results in various genomic changes that ultimately may give rise to tumorigenesis and the development of hematological malignancy [37]. Here, alterations in C-NHEJ and A-EJ components are separately discussed in four categories: leukemia, lymphoma, myelodysplastic syndromes (MDS), and multiple myeloma (MM).

Leukemia

Genomic instability is one of the key drivers of hematological malignancy and is responsible for leukemia progression [38]. Genomic instability, including mutations in DNA sequences, chromosomal aneuploidy, translocations, and gene amplifications, are frequently found in leukemia cells suggesting that the DSB response may be altered. A growing body of evidence showed that dysregulation of DSB repair pathways could predispose patients to different leukemia. Deficiencies in DNA repair pathways are causal factors for many solid cancers, but they are only just beginning to be explored in leukemia. Here, changes in the DSB repair pathway in leukemia, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) are described in detail.

CLL

Pathogenesis of CLL is characterized by specific genetic abnormalities and changes in cellular signaling pathways. In particular, a disrupted DDR plays the main role in increasing CLL cell survival. Many studies assessed the expression of genes involved in the repair pathway to test how the DSB-repair deregulations are involved in the initiation and progression of the CLL. The elevated levels of MMEJ factors have been observed in B-CLL cells and it was concluded that CLL-specific increased expression levels of the MMEJ factors Lig I and XRCC1 associated

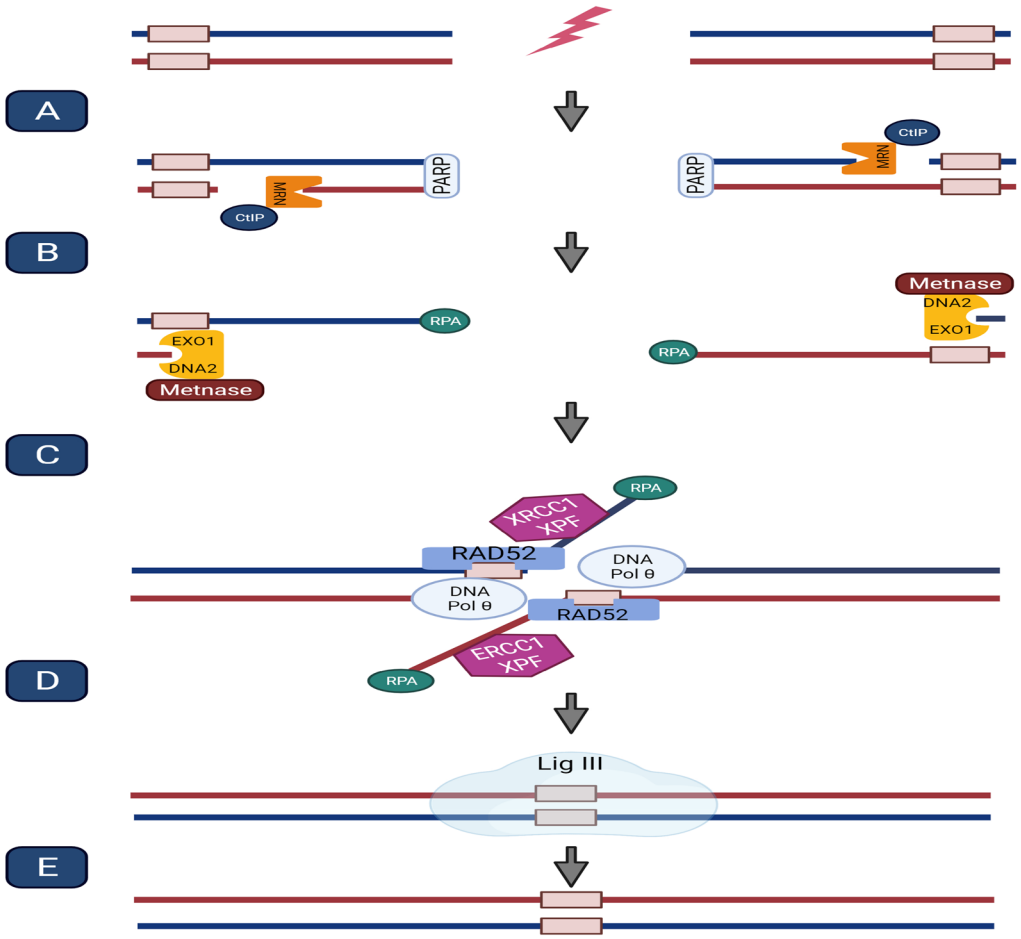

Fig. 3 Alternative non-homologues end joining pathway. **A** PARP1 binds to single-strand DNA for the recognition of damages. It catalyzes the poly-ADP-ribosylation of proteins at DNA damage sites. Also, it contributes to the initial assembling of the MRN complex on DSBs, leading to the activation of ATM and ATR kinases. **B** In SSA, the combination of MRN and CtIP creates short ssDNA, and then, EXO1 or BLM/DNA2 endonuclease complex causes an extensive end resection. EXO1 is loaded on ssDNA by Metnase. **C** RAD52 binds to the RPA-coated single strand annealing the complementary regions. ERCC1/XPF complex removes the tails. This step of DNA end resection is dispensable for MMEJ. **D** Then, polymerases, flap endonucleases, helicases, and polynucleotide kinases prepare the DNA ends for ligation (the gap-filling component of SSA is unidentified). **E** Finally, Lig III ligates the DNA ends with the help of XRCC1 as a scaffolding protein

with an increased chance of gaining chromosomal aberrations throughout DSBR [6]. Klein et al. assessed the associations between the expression levels of proteins regulating apoptosis (BCL-XL and BCL-2) and DNA repair in B-CLL cells and normal B cells. They found a close relationship between Bcl-xL and Bcl-2 expression and Ku80 levels suggesting that in B-CLL cells, modulators of the apoptosis and DNA repair are regulated in a coordinated manner [39]. In another study, CLL cells demonstrated a significantly lower frequency of cells staining positive for DNA-PKcs and Ku86, but not for Ku70, in comparison with ALL cells. Surprisingly, MM samples were reported to express significantly higher DNA-PKcs, Ku86, and Ku70 protein levels compared to CLL. Therefore it was suggested that DNA-PK expression coincides with the degree of lymphoid malignant cells maturity [40]. DNA-PKcs was also shown to be overexpressed in CLL patients with del(17p) and del(11q), indicating that DNA-PK may contribute to disease progression. Moreover, these data support the hypothesis of targeting DNA-PKcs in poor-risk CLL and demonstrate a validation for the use of a DNA-PK inhibitor [41].

Analysis of DNA-binding activity of the Ku70/80 heterodimer showed an increased DNA-binding activity in the resistant B-CLL cells compared to the sensitive cells (before and after irradiation treatment). Elevated levels of DNA end-binding by the Ku70/Ku80 heterodimer up-regulate DNA-PKcs and NHEJ activity and facilitate

the escape of resistant B-CLL cells from apoptosis even in the presence of irradiation-induced DNA damage [42].

Accumulation of DNA damages and error-prone DNA repair are critical features of genetic instability that are believed to be involved in the pathogenesis of CLL [43]. Although the role of ATM in signaling to repair proteins is associated with a function that could result in resistance mechanism against the alkylating agents, unexpectedly, the loss of ATM protein is consistent with a poor prognosis and aggressive disease in CLL. Austen et al. analyzed 155 CLL cases for ATM mutations, and they found that two-thirds of the medically treated patients with ATM mutations were clinically refractory to DNA damaging chemotherapeutic drugs. A hypothesis suggests that, as ATM can act upstream of p53 in response to DSB to stimulate cell cycle arrest and apoptosis, loss of ATM mitigates the p53-dependent cell death, resulting in a chemo-refractive phenotype [44].

Moreover, telomere length is a prognostic indicator in CLL patients. Short-dysfunctional telomeres can cause illegitimate end-to-end telomeric fusions of chromosomes, leading to genomic instability and disease progression in CLL. A recent study has elucidated the role of C-NHEJ and A-EJ in mediating telomere fusions and suggested that therapeutic agents targeting these DNA repair pathway factors may efficiently sensitize CLL B-cell clones with telomere dysfunction to improve outcomes in patients [45].

ALL

ALL is the most common childhood leukemia and the foremost cause of childhood tumor deaths. During recent decades the occurrence rate of ALL has grown around 30%, whereas the age-standardized incidence rate has stayed almost unchanged. Among all risk factors, smoking has been found to be the chief factor contributing to mortality of ALL cases, therefore, avoiding exposure to carcinogens is of a great importance. Moreover, the high body mass index is another critical factor role-playing in ALL patients' death [46]. Although most pediatric ALL patients respond well to chemotherapy, the outcome becomes less favorable when patients relapse. Cytogenetic alterations are common, and some molecular markers have been recognized to predict the prognosis [47, 48]. Researches revealed that chromosomal translocations that appear prenatally are the primary event in multistage leukemia development. These translocations give rise to gene fusions, such as BCR-ABL and TEL-AML1, which generate altered proteins. Alterations of DNA repair pathways have also been examined in ALL. Using a sensitive approach that is based on automated enumeration of DSB co-localizing proteins γH2AX and 53BP1, a higher γH2AX/53BP1 foci were detected in ALL patients harboring BCR-ABL or TEL-AML1 than patients without gene fusions, suggesting that BCR-ABL/TEL-AML1 induces DNA instability through facilitating further genetic alterations which drive leukemogenesis [49].

AT is a cancer-predisposing disease that individuals are born with two mutated copies of the ATM gene. Patients develop mostly, leukemia and lymphoma. A higher prevalence of chromothripsis (several clustered chromosomal rearrangements in one or few chromosomes) was reported in the genomic landscape of ALL arising in individuals with AT, probably due to the related deficiency in ATM mutation [50]. Similar to AT syndrome, Nijmegen breakage syndrome (NBS) is a cancer-predisposing disease of childhood, resulting from mutations in the NBS1 protein of the MRN complex. Children with NBS usually have concomitant hematologic malignancies, including ALL, T-cell prolymphocytic leukemia (T-PLL), and non-Hodgkin lymphoma (NHL) [51–54]. Mutations in Lig IV, which was associated with reduced and less proficient NHEJ, have also been reported in ALL patients [55]. In both murine and human T-ALL cells, the incidence of KRAS mutations associate with the increased expression of A-EJ factors, including DNA Lig IIIa, PARP1, and XRCC1 [56].

Some studies report a correlation between upregulated DNA repair and the stage of the disease in ALL. Using Real-time PCR, Chiou et al. assessed the mRNA transcript of some NHEJ members, including Ku70, Ku80, DNA-PK, Artemis, XRCC4, Lig IV, and Cernunnos/XLF in pediatric ALL patients at different phases of the disease. Compared to thalassemia patients, which were considered control samples in this study, the mRNA expressions of all NHEJ factors were elevated in untreated fresh ALL. After the therapy and once patients achieve complete remission, overexpressed NHEJ mRNAs were downregulated. However, mRNA expressions of Ku80, DNA-PK, Artemis, XRCC4, and DNA ligase IV were raised again in relapsed cases [57]. In another study, only 22% of adult ALL patients with high Ku80 expression achieved durable complete remission compared with 62% of low expresses, suggesting that Ku80 might contribute to poor prognoses in adults with ALL [58].

Polymorphisms in DNA repair genes may modify protein function and cell's capability to repair damaged DNA. There seems to be a correlation between childhood leukemia and a specific polymorphism in the XRCC6 promoter (T-991C). Previous studies have shown that patients harboring TC genotypes are predisposed to a higher risk of childhood leukemia compared to those harboring TT wild-type genotypes [59]. Similarly, XRCC1 (Arg194Trp) polymorphism increases the risk of leukemia. However, the outcomes are different in various studies. For instance, an increased risk of childhood

ALL was reported in an Egyptian population, especially in females [60]. In contrast, no association was found between XRCC1 polymorphisms and increased risk of ALL in a Mexican pediatric population [61]. In patients who developed therapy-related-acute promyelocytic leukemia (t-APL) following mitoxantrone treatment of multiple sclerosis (MS), a marked linkage with 1572G > A polymorphism in *XRCC5* gene has been observed [62]. It is noteworthy that homozygous variants of BRCA2 and XRCC5 are associated with a greater risk of secondary acute promyelocytic leukemia (APL). Likewise, some polymorphisms in both *XRCC5* and *XRCC6* genes increased the risk of leukemia in a Chinese population [63].

AML

AML is the most common adult acute leukemia with variable prognosis, based on the cytogenetic features. The occurrence rate of AML exhibits an increasing pattern, in which males and elderly people are the most probable cases to develop AML. Regarding age among AML patients, a comparison of developing and developed countries betokened a higher mortality rate in the latter [64]. AML is classified as a heterogeneous clonal neoplasm in which different translocations and mutations are involved. Moreover, recurrent mutations in genes such as FLT3, TP53, CEBPA, NPM1, RUNX1, IDH1/2, DNMT3A, KMT2A, and ASXL1 exacerbate the burden of the disease [65]. Given the increased incidence of AML, targeted and effective therapeutic approaches are required to lower the burden of this disease.

Genetic and epigenetic changes can trigger aberrant DNA damage response in AML cells and induce disease progression and resistance to chemotherapy [66, 67]. Many research studies have correlated recurrent chromosomal translocations distinctive of AML with DNA repair defects. As mentioned earlier, NBS1 mutations expose the genome to a series of risks. A case study has reported that treatment of T-cell NHL in a pediatric NBS patient with DNA topoisomerase II inhibitors has led to a secondary MLL-positive acute monocytic leukemia. This finding suggests that dysfunction of NBS1 may contribute to NHEJ-mediated MLL alterations, especially in patients treated with DNA-damaging agents [68]. In addition, younger age and topoisomerase II inhibitors seem to be implicated in predisposition to t-AML with MLL rearrangements [69]. Oncogenic K-RAS mutations also direct DSB repair in AML cells towards the error-prone A-EJ pathway, and blockage of this pathway could be a potential target in K-RAS mutated cells [56, 70].

Although germline mutations in DSB repair genes are infrequent, transcriptional deregulation and common polymorphisms can predict the patient's risk to DNA damage and, therefore, the susceptibility to AML development [66]. Compared to mobilized peripheral blood CD34 + progenitor cells from healthy donors, myeloid leukemia cells display elevated activities of error-prone NHEJ and A-EJ pathways [71]. The overexpression of both PARP1 and Lig III markedly favors two or more simultaneous translocations in AML, whereas the patients with one isolated translocation showed overexpression of Lig III alone [72]. AML patients bearing MLL translocations have an intermediate-to-poor prognosis (5-year disease-free survival of 30%-60%), and their leukemia cells are often resistant to conventional chemotherapies. It was shown that PARP1 contributes to the maintenance of MLL-AF9 leukemias. Interestingly, PARP1 inhibition enhances chemosensitivity toward DSB-inducing agents such as cytarabine and doxorubicin in MLL-AF9–positive AML cells [73]. As stated earlier, in FLT3/ITD-positive AML cells, the c-Myc expression is elevated, which in turn contributes to the augmented expression of A-EJ factors, especially PARP1 and Lig III [74]. Strikingly, in FLT3/ITD + cell lines and murine FLT3/ITD bone marrow mononuclear cells, the down-regulation of Ku70/80 was coupled with the upregulation of DNA Lig IIIα. Given that FLT3/ITD expression resulted in augmented A-EJ repair, these DNA repair modules constitute appealing targets for developing novel therapeutic approaches in combination with FLT3 inhibitors [75]. SIRT1, a protein directly deacetylating and activating Ku proteins, is another mediator, responsible for the upregulation of C-NHEJ components [76]. Ten-Eleven Translocation-2 (TET2), a member of the TET family of enzymes, has key roles in epigenetic regulation and the occurrence of hematopoietic diseases. It was shown that TET2 overexpression might account for the increased mRNA expression of Lig IV in the HL60 cell line [77, 78]. Likewise, both Lig IV and DNA-PKcs are elevated in daunorubicin (DNR)-resistant HL60 cells [79]. Overall, the upregulation of DSB repair genes facilitates the escape of AML cells from the DNA damage response (DDR) anticancer barrier and causes chemotherapy resistance.

Various polymorphisms in DSB repair genes have been associated with an increased risk of AML development or disease relapse. XRCC1 Arg399Gln and XRCC1 Arg194Trp are the two polymorphic variants of XRCC1 reported in AML patients, associated with downgraded DNA damage repair function [80, 81]. A higher frequency of both XRCC1 polymorphic variants was reported in AML patients. Additionally, both of the variants were also contributed to better overall survival, suggesting that defects in DNA repair elements could influence the predisposition of leukemic cells to chemotherapy treatment [80]. However, Seedhouse et al. observed no correlation between the XRCC1 Arg194Trp genotype and

AML/t-AML pathogenesis, and instead, they recognized that XRCC1 Arg399Gln was protecting for t-AML [82]. A meta-analysis study reported no association between XRCC1 polymorphisms and the chance of AML development [83].

CML

The leukemic clone of CML originates from a hematopoietic stem cell (HSC) by gaining the chromosomal translocation t(9;22)(q34;q11) containing the BCR-ABL1 fusion gene. CML is characterized by a primary chronic phase that progresses to an accelerated phase and a lethal blast phase [84]. Throughout this course of progress, the activated BCR-ABL1 tyrosine kinase (TK) stimulates various oncogenic pathways (e.g., PI3K/AKT, JAK/STAT), driving malignant differentiation [85]. Therefore, BCR-ABL1 kinase-mediated genetic instability apparently plays a key role in the blastic transformation of CML [86]. SIRT1, an overexpressed protein in CML patients, which can regulate the expression of Ku70 through NHEJ, has a close correlation with the acquisition of BCR-ABL mutations [87]. It was shown that the mechanism involved in the t(9:22) translocation resulting in BCR-ABL1 is frequently due to the SSA and NHEJ [88]. Also, BCR-ABL induces reactive oxygen species (ROS) formation. Subsequently, these species destabilize the genome through unfaithful HR and NHEJ-induced DSBs in proliferating cells [89]. Unfaithful NHEJ-mediated BCR-ABL repair, characterized by the decreased levels of Lig IV and Artemis, but not DNA-PKcs, is compensated by the upregulation of Lig III and WRN proteins [90]. Moreover, by overexpression of c-Myc in leukemic cells, BCR-ABL1 increases the expression of A-EJ factors, including Lig III and PARP1 [74]. K562, a BCR-ABL-harboring cell, shows an increase in WRN and Lig III at the protein level. This overexpression has also been observed in P210MO7e cells, as well as CML patients [91]. Loss of ATM function (even monoallelic loss) was also accelerating the blast crisis in BCR-ABL-expressing CML cells [92]. Overall, the Philadelphia chromosome arises from DSB misrepair through ineffective NHEJ [91, 93].

Lymphoma

Lymphomas are fundamentally divided into two main groups: Hodgkin lymphoma (HL) and NHL. B-cell NHL frequently exhibits recurrent reciprocal translocations, which commonly involve a juxtaposition of immunoglobulin heavy chain (IgH) loci by a proto-oncogene (e.g., BCL2 and BCL6) [94]. Likewise, the development of HL is partially followed by adverse alleles in base excision repair (BER) and DSBR genes, such as XRCC1, the main factor of MMEJ [95]. Also, the rapid development of lymphoma in Lig $IV^{-/-}p53^{-/-}$, $XRCC4^{-/-}p53^{-/-}$, $Ku80^{-/-}p53^{-/-}$, and $DNA\text{-}PKcs^{-/-}p53^{-/-}$ mice supports the notion that lymphomagenesis is increased by NHEJ loss, especially if the p53 activity is impaired [96].

Oncogenes sometimes have a direct impact on DSBR or may be indirectly involved in DSBR by affecting the progression of the cell cycle and the production of ROS. Oncogenic expression of RAS and suppression of ATR synergistically increase genomic instability in AML caused by MLL-ENL [97], as well as c-Myc-driven lymphoma [98]. Myc plays a key role in increasing the A-EJ activity in TK-activated leukemia through transcriptional and post-transcriptional changes in Lig III and PARP1 [99]. It is known that c-Myc exerts two paradoxical effects on cancer. First, it induces DDR to recognize and repair the damage through ATM/CHK2, leading to tumor suppression. Second, it modulates replication stress through the ATR/CHK1 pathway and protects cancer cell viability [100].

In diffuse large B-cell lymphoma (DLBCL) cells, the expression of key MMEJ proteins, including Lig I, Lig III, PARP1, CtIP, and MRE11 elevates, while the level of C-NHEJ factors decreases [101]. SUDHL8, a cell line driven from a DLBCL patient, showed the increased expression of XRCC6 by four to five folds and the reduced expression of MRE11 by two folds, compared to benign reactive lymphocytes. This pattern not only can be seen in DLBCL but is also consistently observed in other mature B cell lymphomas, including follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL) [102]. Epstein–Barr virus (EBV)-driven NK/T lymphoma also has a profile of downregulated Cernunnos (XLF) [103].

Mutations in DDR genes, including Artemis, DNA-PKcs, Ku70, Ku80, CHK2, and PARP1, have also been reported in DLBCL [104]. Through inactivation of ARF and p53, two potent tumor suppressor proteins, mutated ATM contributes to tumorigenesis [105]. Besides quantitative mutations, qualitative or functional mutations are also observed in NHEJ factors, including Artemis, DNA-PKcs, XRCC5/Ku80, and XRCC6/Ku70, especially in DLBCL with translocations [104]. MCL, another NHL, refers to an aggressive hematologic malignancy with a poor prognosis. Statistical analysis revealed that 26% of MCL cases had p53 mutation/deletion, 56% showed ATM alterations, and 10% showed both alterations. The p53 mutation status is correlated with the extent of cell response to PARP and ATM targeting [106, 107]. Although ATM alteration is mostly observed in B-CLL, MCL, and T-PLL, it has also been infrequently identified in DLBCL, FL, and rarely, adult ALL [108]. Also, a particular subtype of MCL, leukemic non-nodal MCL, is associated with the deletion of PARP1 [109]. Finally, activation-induced cytidine deaminase (AID),

which is responsible for DSB generation in CSR, plays an important role in the generation of Ig-partnered chromosome translocations in many B cell lymphomas and leukemias. Also, AID can be a source of secondary mutations in some types of human cancers, such as ALL and CML, thereby contributing to tumor progression [110].

The presence of T-nucleotides at t(11;14)/CCND1-IgH junction in MCL suggests the involvement of an aberrant V(D)J recombination and NHEJ or A-EJ repair pathways in MCL. A similar finding has also been reported at t(14;18)/IgH-MALT1 in mucosa-associated lymphoid tissue (MALT) lymphoma and at t(14;18)/IGH-BCL2 in FL [111]. Correspondingly, t(11;18)(q21;q21) translocation of MALT lymphoma may be the consequence of aberrant NHEJ following DSB [112].

MDS

Several studies have shown that MDS cases are at significance risk of transforming into AML. Various predicting factors, such as mutations in NRAS, KRAS, PTPN11, FLT3-ITD, NPM1, WT1, and IDH2, as well as monosomy 7, complex karyotype, and loss of 17p have been found to be related to MDS transformation into AML [113, 114]. MDS refers to HSC diseases and is characterized by an elevated NHEJ activity [115]. De Laval et al. showed that upon exposure to ionizing radiation, TPO promotes C-NHEJ in stem and progenitor cell populations through binding to its receptor (MPL), thereby initiating MDS; however, this TPO/DNA-PK-mediated NHEJ repair pathway in HSC may be defective [116, 117]. It was shown that downregulation of some NHEJ factors, such as Lig IV, Ku70, and Ku80, are involved in primary MDS [118]. Besides, the expression level of PARP1, an A-EJ factor, has been newly approved as a prognostic factor of MDS. PARP1 mRNA expression was shown to be the only biomarker of response to hypomethylating agents (HMAs) 5-azacytidine in patients with MDS. Patients with higher PARP1 mRNA levels had a better response to 5-azacytidine and longer median survival after treatment initiation, suggesting that PARP1 can potentially serve as a guide to therapeutic decisions [119]. However, it exhibits an inverse correlation with prognosis in AML [120]. Other factors, such as ATM, XRCC6, and Lig IV, are also overexpressed in MDS patients as a consequence of some functional polymorphisms in their germlines [121, 122].

MDS patients, especially patients with late refractory anemia with excess blasts (RAEB-1), exhibit a high expression of phosphorylated ATM, phosphorylated Chk2, and γH2AX, according to the immunostaining analysis [123, 124]. These patients and other high-risk MDS patients have mutations in CtIP and MRE11, which lead to microsatellite instability [125]. These findings not only disclose the role of genomic instability in MDS, but also propose some biomarkers for MDS, as they remarkably accord with γH2AX. The γH2AX level is generally considered a biomarker of DSB and is especially altered in therapy-related MDS (t-MDS). It is known that t-MDS is caused by DSB inducers, such as etoposide, and NHEJ acts as the main route for the repair of etoposide-induced DSB [126]. Collectively, γH2AX and 53BP1 localization in MDS are considered useful biomarkers of the increased level of NHEJ [123].

MM

MM is a B cell neoplasm of the bone marrow characterized by various clinical presentations, including anemia, bone lesions, infection, hypercalcemia, and renal insufficiency [127]. Mutations in ATM, ATR, MRN complex, XRCC3, XRCC4, and BRCA1, as well as DDR ubiquitin ligase, RNF168, are continuously reported in MM [128, 129]. Both NHEJ and HR mechanisms have shown to be aberrantly upregulated in myeloma cells. In this regard, Herrero et al. observed the upregulation of DNA-PKcs, Artemis, and XRCC4 in MM. They also reported an upregulation of the A-EJ protein DNA ligase IIIα in plasma cells isolated from patients with MM [130]. Compared to normal B cells, a compelling body of evidence shows that the expression of XRCC6 is downregulated in MM and other lymphoma cells. However, unlike XRCC6, there is an increase in the expression level of XRCC4 in MM patients, compared to mature B cell lymphomas, such as MCL, FCL, and DLBCL [102].

Moreover, the increased expression of XRCC4 and Lig IV has been observed in a melphalan-resistant cell line [131]. There is also an elevation in the expression of XRCC5 and Artemis genes in MM cells, compared to monoclonal gammopathy of unknown significance (MGUS) plasma cells [132]. The expression of other components, such as ERCC1, has recently attracted the researchers' attention, considering its association with sensitivity to melphalan and cisplatin. Additionally, overactivation of A-EJ components, especially Lig IIIa, has been frequently observed in MM cells [133]. Despite previous reports, knowledge in this field is still limited, and further studies are required. Table 1 summarizes the NHEJ alterations in hematologic malignancies.

Treatment of hematologic malignancies by targeting the components of DSBR:

Malignant cells, which are defective in one pathway, are dependent on other pathways; accordingly, many studies have applied a targeting strategy against these pathways. Several studies revealed that repair knockout mouse models display developmental deficiencies, suggesting that repair proteins have numerous functions. In this regard, it should be noticed that the chemical inhibition

Table 1 Alterations of NHEJ (classical or alternative) level in hematologic malignancies

Type of malignancy	Subtype of malignancy	Involved factor ↑ = **Increase** ↓ = **Decrease**	Highlights	Ref
Leukemia	FLT3/ITD-positive AML	↓ Ku70/80, ↑ PARP-1 and DNA Lig IIIα	Disease progression and Chemoresistance	[75]
	APL	Homozygous variants of BRCA2 and XRCC5	Risk of secondary APL development	[62]
	MLL-rearranged AML	↑ PARP1	Maintenance of MLL-AF9 in Leukemia	[73]
		Coexistence of NBS1 and MLL mutations	Increase chance of secondary malignancy after treatment with DNA topoisomerase II inhibitors	[68]
	K562/DNR	↑ DNA-PKcs and Lig IV	DNR resistant More aggressive MDR phenotype	[79]
	CML	↓ DNA-PK, Lig IV, and Artemis ↑ Lig III and WRN	Progression to blast crisis	[91, 134]
	K562 cells (BCR-ABL^{+})	↑ WRN and Lig III ↓ Artemis	Increased repair infidelity and survival of leukemic cells	[91, 93]
	ALL	Mutations in LIG IV, ATM, and NBS1	Development of disease	[50, 51, 135]
		↑ mRNA of Ku70, Ku80, DNA-PK, Artemis, Lig IV XRCC4, and Cernunnos ↑ 53BP1/γH2AX foci	Unfaithful DSBR and increased genome instability Causing BCR-ABL and TEL-AML fusions	[57, 70, 136]
		Polymorphisms in XRCC6 and XRCC1	Ethnic-dependent increased risk of ALL	[59, 60, 137]
	KRAS-mutant T-ALL	↑ DNA Lig IIIα, PARP1, and XRCC1	Hyperactivation of more error-prone pathways (A-EJs)	[138]
	T-ALL	↑ PI3K/mTOR pathway (ATM-ATR-DNA-PK)	Poor prognosis and failure of treatment	[139]
	CLL	↑ MMEJ factor and DNA-PK	Poor survival of patients	[6, 42]
		Mutation or deletion of ATM	Chemoresistance	[140]
		↑ SSA	Telomere fusion	[45]
Lymphoma	C-MYC-driven lymphoma	↑ ATM/CHK2 ↑ ATR/CHK1	Paradoxical effects, including tumor suppression and protection of the viability of cancer cells	[100]
	Mature B cell lymphoma (FL, MCL, DLBCL, MALT, and MZL)	↑ Lig I, Lig III, PARP1, CtIP, and MRE11 ↓ C-NHEJ functional mutations in Artemis, DNA-PKcs, XRCC5, and XRCC6	High level of DSB and aberrant DSBR	[101, 102]
	DLBCL	Mutations in ATM	Inactivation of ARF as a tumor suppressor gene and P53	[141]
	Leukemic non-nodal MCL	Deletion of PARP1	Unfavourable outcome	[109]
	EBV-driven NK/T lymphoma	↓ Cernunnos (XLF)	Genomic instability	[103]
	HL	Adverse alleles of DSBR genes, including XRCC1	Genomic chaos Dicentric chromosomes resulting from telomere dysfunction and aberrant NHEJ	[142, 143]
MDS	MDS	↑ Defective C-NHEJ ↑ A-EJ ↓ Lig IV, Ku70, and Ku80	A contingently ineffective increase in C-NHEJ	[118, 144]
MM	MM	↑ DNA-PKcs, Artemis, XRCC4, and Lig IIIa ↓ XRCC6 ↑ Lig IV and XRCC4 Mutations in ATM, ATR, MRN complex, XRCC3, and XRCC4	Ineffective increase of C-NHEJ pathway	[77, 128–130]
		ERCC1	Prediction of response to melphalan and cisplatin	[133]

of repair protein components presents a totally different scenario compared to gene knockouts. Chemical inhibitions are applied in shorter durations and localized manner [145]. Here, we conducted an elaborated review of different inhibitors against NHEJ, which can be used as a treatment strategy for hematologic malignancies. Also, a thorough status of clinical trials of these inhibitors for blood malignancies has been listed in Table 2.

PARP1 inhibition

A-EJs are considered the main cause of translocation. PARP1 by initiating A-EJ seems to be associated with chromosomal translocations. PARP1 inhibition can hinder both ionizing radiation (IR)-generated and topoisomerase II inhibitor-generated translocations [146]. Since Pol θ depletion can increase sensitivity to PARP inhibition, it can serve as a biomarker, indicating the extent of cell response to PARP1 inhibitors [147, 148]. Both quiescent and proliferating leukemia cells are sensitive to PARP1 inhibitors. Therefore, leukemia stem cells and progenitor cells involved in leukemia can be therapeutic targets [149].

The combination of FLT3 and PARP1 inhibitors eliminates both quiescent and proliferating FLT3-ITD-positive AML cells [150]. Response to a PARP inhibitor, olaparib (AZD2281, MK-7339), has been evaluated in MCL cells deficient in both ATM and p53 and the cells lacking ATM function alone. The results showed that ATM- and p53-deficient cells are more sensitive than ATM-deficient cells to olaparib, indicating that p53 regulates the response of ATM-deficient MCL cells to Olaparib [106]. In contrast, PARP1 inhibition by AG14361 in MCL cell lines shows potent cytotoxicity in combination with topotecan in a p53-independent manner [151].

Tobin et al. demonstrated that the combination of PARP1 with Lig III inhibitors could reduce the survival of CML cells, with the effect being greater in imatinib-resistant CML cells, which express higher levels of PARP1 and Lig III [152]. Moreover, given the remarkable effects of PARP1 inhibitors on the treatment of tumors with decreased levels of BRCA [153], it can be suggested that these inhibitors are beneficial in hematologic malignancies with a reduced BRCA profile, such as CML (Fig. 4) [154].

While some adult T-cell leukemia (ATL) cells are sensitive to PARP inhibitor PJ-34 due to caspase 3-dependent apoptosis, the MT-2 cells (an ATL cell line) are resistant. Augmented expression of BRCA1 or p53-binding protein 1 (P53BP1) has been reported to associate with resistance to PARP inhibitors. However, expression levels of p53BP1 or BRCA1 were not influenced in HTLV-I-transformed MT-2 before or after PJ-34 treatment [155]. PJ-34 has also been shown to be effective in suppressing the proliferation of HL60, MOLT4, and K562 cell lines, but not U937 cells when used in combination with a histone deacetylase inhibitor, vorinostat [156]. The PARP inhibitor also induces synthetic lethality in AML [157]. In a subgroup of AML patients, including those with AML1-ETO translocation, PARP1 inhibitors may be applicable. As mentioned earlier, maintenance of MLL-rearranged AML cells can be a result of PARP1 function. Therefore, PARP1 inhibition by olaparib and talazoparib (BMN-673) in MLL-AF9 leukemia cells increases the number of DSBs, the rate of cell death, and treatment efficacy in combination with conventional therapies [73]. The results of an ex vivo study showed that talazoparib induced a significant inhibitory effect on the proliferation of CLL cells, regardless of the ATM level [158].

Evidence suggests that ATM-deficient tumors are more sensitive to PARP inhibitors. Likewise, ATM-defective CLL cells have a hypersensitive pattern for PARP inhibitors compared to the ATM-proficient counterparts [159]. However, according to some conflicting results, since acetylation inhibits DNA repair factors, and hypomethylation is in favor of hyperacetylation, a combination of a hypomethylation agent with PARP inhibitors can induce apoptosis in human leukemia and lymphoma cells through acetylation of Ku70, Ku80, PARP1, ERCC1, and XPF [160]. Also, veliparib (ABT-888) is a PARP inhibitor with favorable effects against advanced lymphoma and MM when used in combination with bendamustine and rituximab [161].

The results of an in vitro study demonstrated that the combination of ABT-888 with a CDK inhibitor, dinaciclib, is effective in the induction of cell death in MM cells; however, this combined treatment did not exert any cytotoxic effects against normal CD19 + B cells [162]. Phase I trial of the PARP inhibitor veliparib and metronomic cyclophosphamide in patients with low-grade lymphoma showed promising results [163]. Several trials are testing the effectiveness of veliparib in combination with chemotherapeutic drugs, including Phase I trial of ABT-888 with cyclophosphamide and doxorubicin in NHL [ClinicalTrials.gov Identifier: NCT00740805] and phase I trial of ABT-888 with bortezomib and dexamethasone in patients with relapsed refractory myeloma in [ClinicalTrials.gov Identifier: NCT01495351]. On the other hand, a promising response rate to veliparib in combination with topotecan and carboplatin was achieved in patients with aggressive myeloproliferative disorders [164].

Niraparib (MK4827), another PARP1 and PARP2 inhibitor, is in the clinical trial phase for use in monotherapy against CLL and T-PLL [ClinicalTrials.gov Identifier: NCT00749502]. Since MCL is an aggressive malignancy, efforts have been made to find a suitable drug against this disease. CEP-9722 (paralog cep-8983) is

Table 2 Overview on clinical trials of hematological malignancies treated with DNA repair inhibitors

Target	Conditions	Compound	Phases	Participants	Status	NCT Number
PAPR	Myelodysplastic Syndrome and Acute Myeloid Leukemia Related to PARP Inhibitors (MyeloRIB)	PARP Inhibitors	–	178	Completed	NCT04326023
	Acute Lymphoblastic Leukemia Acute Myeloid Leukemia	Veliparib (ABT-888) Temozolomide	Phase 1	66	Active, not recruiting	NCT01139970
	Acute Myeloid Leukemia Recurrent Myelodysplastic Syndrome	Olaparib	Phase 2	94	Recruiting	NCT03953898
	Leukemia Lymphoma	veliparib	Phase 1	23	Completed	NCT00387608
	Chronic Lymphocytic Leukemia T-cell-prolymphocytic Leukemia	Niraparib (MK4827)	Phase 1	113	Completed	NCT00749502
	Acute Myeloid Leukemia Myelodysplastic Syndrome Chronic Lymphocytic Leukemia Mantle Cell Lymphoma	BMN-673 (talazoparib)	Phase 1	33	Completed	NCT01399840
	Leukemia	BMN 673	Phase 1	12	Recruiting	NCT03974217
	Acute Myeloid Leukemia	BMN 673 Decitabine	Phase 1 Phase 2	25	Active, not recruiting	NCT02878785
	B-cell Malignancy, Low-grade	E7449 (dual PARP1/2 and TNKS1/2 inhibitor) alone E7449 plus TMZ E7449 plus carboplatin and paclitaxel	Phase 1 Phase 2	41	Completed	NCT01618136
	Adult Acute Megakaryoblastic Leukemia Adult Acute Myeloid Leukemia Chronic Myelomonocytic Leukemia Essential Thrombocythemia Myelodysplastic Syndrome Philadelphia Chromosome Negative, BCR-ABL1 Positive Chronic Myelogenous Leukemia Polycythemia Vera Recurrent Adult Acute Lymphoblastic Leukemia	Veliparib Topotecan-Hydrochloride Carboplatin	Phase 1	12	Active, not recruiting	NCT00588991
	Acute Myeloid Leukemia Atypical Chronic Myeloid Leukemia, BCR-ABL1 Negative| Chronic Myelomonocytic Leukemia| Essential Thrombocythemia| Myelodysplastic/Myeloproliferative Neoplasm| Myelofibrosis| Polycythemia Vera|	Veliparib Topotecan-Hydrochloride Carboplatin	Phase 2	60	Suspended	NCT03289910
	Leukemia| Lymphoma| Waldenstrom Macroglobulinemia|	Veliparib Rituximab Bendamustine-Hydrochloride	Phase 1 Phase 2	43	Completed	NCT01326702
	Mantle Cell Lymphoma	CEP-9722 Gemcitabine Cisplatin	Phase 1	24	Completed	NCT01345357

Table 2 (continued)

Target	Conditions	Compound	Phases	Participants	Status	NCT Number
DNA-PK	Chronic Lymphocytic Leukemia	CC-115	Phase 1	118	Completed	NCT01353625
	Refractory/Recurrent Acute Myeloid Leukemia	MSC2490484A (M3814) Mitoxantrone Etoposide Cytarabine	Phase 1	48	Recruiting	NCT03983824
	Chronic Lymphocytic Leukemia	MSC2490484A (M3814)	Phase 1	31	Completed	NCT02316197
	Lymphoma, Non-Hodgkin	CC-122 (Avadomide)	Phase 1	15	Active, not recruiting	NCT02509039
	Large B-Cell, Diffuse Lymphoma, Non-Hodgkin	CC-122 Obinutuzumab	Phase 1	75	Active, not recruiting	NCT02417285
	Diffuse B-Cell Lymphoma	CC-122 RCHOP	Phase 1	35	Completed	NCT03283202
	Leukemia, Lymphocytic, Chronic, B-Cell	CC-122 Ibrutinib Obinutuzumab	Phase 1 Phase 2	47	Completed	NCT02406742
	Multiple Myeloma Lymphoma, Large B-Cell, Diffuse	CC-122	Phase 1	271	Active, not recruiting	NCT01421524
	Lymphoma, Large B-Cell, Diffuse	CC-122 CC-223 Rituximab CC-292	Phase 1	174	Active, not recruiting	NCT02031419
	Lymphoma, Non-Hodgkin Lymphoma, Large B-Cell, Diffuse Lymphoma, Follicular	CC-122 JCAR017 Durvalumab Ibrutinib CC-220 Relatlimab Nivolumab CC-99282	Phase 1 Phase 2	77	Recruiting	NCT03310619
	Chronic Lymphoproliferative Diseases	GRN163L (Imetelstat)	Phase 1	48	Completed	NCT00124189
	Multiple Myeloma	GRN163L	Phase 1	40	Completed	NCT00718601
	Multiple Myeloma	GRN163L	Phase 1	20	Completed	NCT00594126
	Primary Myelofibrosis Secondary Myelofibrosis Myeloid Malignancies	GRN163L	Phase 2	81	Completed	NCT01731951
	Myelofibrosis (JAK-Inhibitor Treatment resistance)	GRN163L Best Available Therapy (BAT)	Phase 3	320	Recruiting	NCT04576156
	Myelodysplastic Syndromes	GRN163L Placebo	Phase 2 Phase 3	225	Recruiting	NCT02598661
	Multiple Myeloma	GRN163L lenalidomide	Phase 2	13	Completed	NCT01242930
	Essential Thrombocythemia| Polycythemia Vera	GRN163L	Phase 2	20	Completed	NCT01243073

Table 2 (continued)

Target	Conditions	Compound	Phases	Participants	Status	NCT Number
ATR	Lymphomas	BAY1895344	Phase 1	241	Recruiting	NCT03188965
	11q-deleted Relapsed/Refractory Chronic Lymphocytic Leukaemia (CLL)| Prolymphocytic Leukaemia (PLL)| B Cell Lymphomas	AZD6738 (Ceralasertib)	Phase 1	2	Completed	NCT01955668
	Leukemia| Myelodysplastic Syndrome CMML	AZD6738	Phase 1	52	Recruiting	NCT03770429
	Chronic Lymphocytic Leukemia	AZD6738 Acalabrutinib	Phase 1 Phase 2	12	Active, not recruiting	NCT03328273
	Cancers	AZD6738 Gemcitabine	Phase 1	55	Recruiting	NCT03669601
	Relapsed/refractory aggressive Non-Hodgkin's Lymphoma	AZD6738 AZD9150 Acalabrutinib Hu5F9-G4 Rituximab AZD5153	Phase 1	30	Completed	NCT03527147

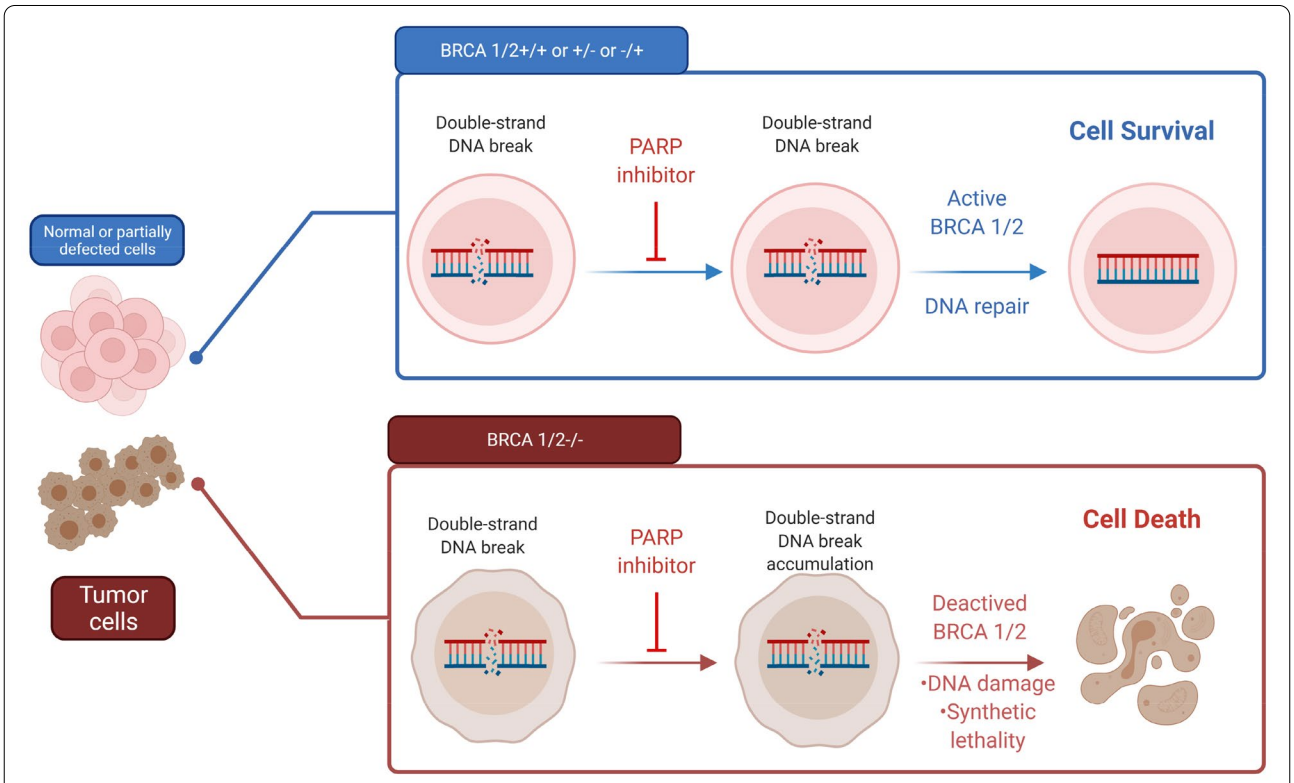

Fig. 4 Cells with normal BRCA1/2 or with one normal allele can compensate for double-strand break repair in the presence of PARP inhibitors. On the other hand, using PARP inhibitors in tumor cells with double-negative BRCA1/2 accumulate DSB, which leads to cell death

also a PARP inhibitor, which is currently in phase I clinical trial for the treatment of MCL in combination with gemcitabine and cisplatin [ClinicalTrials.gov Identifier: NCT01345357]. Talazoparib (BMN-673) inhibits both PARP1 and PARP2 [165]. The effectiveness of talazoparib for the treatment of patients with AML and MDS that have a mutation in the cohesin complex is under investigation in phase I clinical trial [ClinicalTrials.gov Identifier: NCT03974217]. Also, preclinical studies on AML mouse models and primary patient samples revealed that the combination of talazoparib with DNA methyltransferase (DNMT) inhibitor decitabine resulted in enhanced cytotoxicity in AML cells [166].

As mentioned earlier, RNA interference is an interlinking issue in DDR. The overexpression of MALAT1, a long non-coding RNA, plays an important role in DNA repair and cell death in MM cells, especially through interaction with PARP1. MALAT1 degradation by RNase H in MM cells results in poly-ADP-ribosylation of nuclear proteins and further stimulation of apoptotic pathways. Considering the anti-cancer effects of anti-MALAT1 therapy in MM cell lines, xenograft murine models and in vivo models have suggested this agent as a novel therapeutic option against MM [167]. Finally, the novel PARP1 inhibitor, P10, has shown significant effects on the human leukemic cell line, Nalm6, where PARP1 and PARP2 are highly overexpressed [168]. Table 3 summarizes PARP1 targeting in hematologic malignancies.

Ku inhibition

Due to the central position of Ku70/80 dimer in NHEJ repair pathways, targeting them seems rational for disrupting the whole pathway. Considering the hyperactivation of the NHEJ pathway in HTLV-1 transformed cells, it looks that targeting Ku70 in these cells can be a suitable therapeutic approach [169]. Since SIRT1 promotes DSBR by deacetylating Ku70 in CML cells, the NHEJ pathway may be impaired through inhibition of SIRT1, which increases Ku70 acetylation [76]. Currently, no small molecule inhibitors against Ku proteins have been developed. However, depletion of Ku70 protein by RNAi technology effectively sensitized the mammary cells to radiation [170–172].

Given the necessity of chromatin remodeling in Ku recruitment, it seems that targeting this process inhibits NHEJ and leads to radio sensitization [173]. The use of HDAC inhibitors, as chromatin remodeling inhibitors, has been approved for patients with refractory cutaneous T-cell lymphoma [174, 175]. In Jurkat T cell lymphoma cells, silencing of Ku70 results in DNA damage accumulation, DDR impairment, reduction of cell proliferation, and induction of cell death; therefore, Ku70 can be a promising target in ATL cells [169].

DNA-PK inhibition

Inhibition of DNA-PK seems an appealing approach to subside resistance to therapeutically induced DNA DSBs, and for this reason, relatively extensive research has been done in this area. Inhibition of DNA-dependent protein kinases enhances ultrasound-induced apoptosis in human leukemia cell lines U937 and Molt-4, regardless of p53 phenotype, suggesting DNA-PK as a promising target for ultrasound-aided therapy [176]. Critical signaling pathways in CLL are hampered by dual mTOR/DNA-PK inhibition, reducing cell survival and proliferation of chemoresistant CLL cells. CC-115, a dual inhibitor of DNA-PK and mTOR, inhibits proliferation and induces caspase-dependent apoptosis in primary CLL cells. Also, the clinical efficacy of CC-115 was demonstrated in relapsed/refractory CLL/small lymphocytic lymphoma patients harboring ATM deletions/mutations [177]. Also, the effect of CC-122, a DNA-PK inhibitor, in NHL and MM is under investigation, and favorable results have been reported in phase I clinical trial [ClinicalTrials.gov Identifier: NCT01421524] [178].

Deriano et al. demonstrated that NHEJ DSB repair is overactivated in human B-CLL cells in the presence of irradiation-induced DNA damage. This allows the escape of B-CLL cells from apoptosis. Moreover, they showed that NU7026, a DNA-PK inhibitor, can sensitize resistant B-CLL cells to irradiation-induced apoptosis [42]. The growth of MOLT-4 leukemia cells has been reported to be hampered by combination therapy, using NU7026 and radiation [179]. In addition, NU7026 promotes the cytotoxicity of topoisomerase II inhibitors in K562 leukemia cells [180]. The promoting effect of DNA-PK inhibitors on radiation and topoisomerase II inhibitors has been demonstrated in several hematologic cancers, such as CLL, ALL, CML, AML, APL, and adult T-cell leukemia/lymphoma [181]. Given the relationship between ATM deficiency and sensitivity to DNA-PKcs inhibitors, the effects of these inhibitors on lymphoma have been investigated [182].

Bleomycin and etoposide are DSB-inducing agents used against several cancers, especially HL and NHL. Also, IC86621, a selective DNA PK inhibitor, exerts significant synergistic effects when used along with bleomycin and etoposide [183]. Moreover, vanillin as a naturally occurring food component has been shown to have antitumor effects, as it can sensitize lymphoblastic TK6 cells to cisplatin through inhibiting the activity of DNA-PK, a crucial NHEJ component [184]. M3814 (MSC2490484A) is another selective DNA-PK inhibitor, which can effectively induce cell death in AML cells by increasing p53-dependent apoptosis [185]. Moreover, the combination of M3814 with Mylotarg (the first AML-targeting drug from a new generation of antibody drug conjugate

Table 3 Pre-clinical studies on PARP1 and DNA-PK inhibitors against hematologic malignancies

Target	Inhibitors	Type of malignancy	Highlights	Ref
PARP1	Olaparib (AZD2281, MK-7339)	MCL and MLL-AF9 rearranged Leukemia cells	Higher sensitivity of double-deficient ATM/p53 MCL cells, compared to mono-deficient MCL cells in ATM	[106]
	AG14361	MCL cells	Enhanced topotecan-induced apoptosis independent of TP53 status	[151]
	PJ-34	Patient-derived ATLL cells	p53-mediated caspase 3-dependent apoptosis	[155]
		HL60, MOLT4, and K562 human leukemia cell lines	Synergistic effect in combination with histone deacetylase inhibitor, vorinostat	[156]
	BMN-673 (talazoparib)	Patient-derived CLL samples	Inhibited the proliferation of CLL cells independently of p53/ATM function	[158]
		Primary AML samples AML mouse models	Enhanced apoptosis in combination with decitabine	[166]
	Veliparib (ABT-888)	Patients with relapsed/refractory lymphoma and MM	Enhances the cytotoxicity of bendamustine and rituximab	[161]
		MM cells MM xenografts in SCID mice	Combined treatment with CDK inhibitor dinaciclib resulted in synthetic lethality of MM cells	[162]
		Acute leukemia, high-risk MPNs	Promising results in Combined treatment with topotecan and carboplatin in phase I study	[164]
	P10	Human leukemic cell line Nalm6	Induction of G2/M arrest and accumulation of DNA damage	[168]
DNA-PK	Wortmannin	Human leukemia cells	Sonolisib (PX-866) is Irreversible wortmannin analogue PWT-458 is PEGylated derivative of wortmannin	[193, 194]
	NU7026	Primary CLL cells	Synergistic effects with chlorambucil	[195]
	CC-115	CLL, NHL, and MM	Phase I clinical trial A dual inhibitor of DNA-PK and mTOR	[177, 196]
	IC86621	NHL and HL	Synergistic effects with bleomycin and etoposide	[183]
	CC-122 (Avadomide)	NHL and MM	Phase I clinical trial	[178, 197]
	NU7441	Pre-B ALL cells	Increase of chemosensitivity to doxorubicin	[198]
	OK-1035	L5178Y cells (lymphoma cell line)	Preclinical testing	[199]
	Dbait (AsiDNA or DT01)	Lymphoma and leukemia cells	32 bp double-stranded DNA fragment that mimics DNA lesion and traps DNA repair enzymes A dual inhibitor of DNA-PK and PARP1	[191]
	GRN163L (Imetelstat)	CLL	Imetelstat sensitizes primary CLL lymphocytes to fludarabine A dual inhibitor of DNA-PK and telomerase	[192]

therapies) in two AML xenograft models, MV4-11 and HL-60, revealed increased efficacy and survival [186]. It should be noted that M3814 is in phase I of a clinical trial for the treatment of CLL patients [ClinicalTrials.gov Identifier: NCT02316197].

Wortmannin is a PI3-kinase inhibitor that also inhibits DNA-PK and thereby impedes DSBs repair [187]. It has been shown that DNA-PK inhibition by wortmannin sensitizes multidrug-resistant (MDR) human leukemia CEM cells (human T-ALL cell line) to chemotherapeutic agents [188]. Akt, a well-known component of the PI3-kinase/Akt/mTOR signaling network, is also a therapeutic target in acute myelogenous leukemia patients and seems to play a role in the phosphorylation of DNA-PK and improving the efficiency of repair [189]. Accordingly, it has been suggested that AKT inhibitors can suppress the phosphorylation of DNA-PK and its activity. Thus, SF-1126, a peptidic pro-drug inhibitor of pan-PI3K/mTORC, has shown satisfactory results against CLL, MM, and NHL in phase I trials [190]. Moreover, PI3K/mTOR overactivation is the cause of relapse in a subtype of pediatric T-ALL; therefore, PKI-587, a dual specificity PI3K/mTOR inhibitor, can be used to inhibit T-ALL cell growth and delay tumor formation [139]. Another novel strategy is to use Dbait (DNA strand break bait) molecules, which mimic DSBs and trap DNA-PK and PARP. Thereby, by generating a false DNA damage signal, they inhibit the recruitment of key repair proteins

at the damage site and ultimately prevent the repair of DNA damage. AsiDNA, a cholesterol form of Dbait, exerts synergistic effects in combination with etoposide, cyclophosphamide, and radiotherapy against lymphoma and leukemia cell lines without increasing their toxicity to normal blood cells [191]. GRN163L (Imetelstat; GRN), a 13-mer oligonucleotide complementary to the template of the TER component of telomerase, is a potent telomerase inhibitor. However, it also inhibits DNA-PK activity and repair of DNA damage. In a recent study by Shawi et al., imetelstat was shown to decrease the fludarabine-induced DNA-PK phosphorylation in primary CLL cells [192]. Table 3 presents the potential targeting strategies against DNA-PK in hematologic malignancies.

ATM inhibition

ATR/ATM kinases are primarily the orchestrators of cellular response to DSB and belong to apical phosphatidylinositol 3-kinase-related kinases (PIKKs). ATM and ATR are predominantly activated through their interactions with NBS1- and RPA-bound single-stranded DNA (ssDNA), respectively [200]. It has been shown that inhibition of ATM and ATR activities promotes survival in xenograft models of AML-carrying MLL rearrangement [201]. KU-55933 was the first developed ATM inhibitor. Mechanistically, KU-55933 impairs the auto-phosphorylation of ATM and concurrently inhibits H2AX phosphorylation. ATM inhibition by KU-55933 sensitized MV4-11 and Jurkat leukemic cells to DSB-inducing agents [202, 203]. It has been shown that inhibition of ATM with two distinct pharmacological inhibitors (namely ATMI and KU55933) induces apoptosis in CD34+positive leukemic blasts through suppression of constitutively activated NF-κB signaling pathway [204].

Lytic reactivation of EBV in latently infected cells induces an ATM-dependent DDR. Therefore, inhibition of ATM activity by KU-55933 during lytic activation of the virus impairs EBV replication in EBV-infected Burkitt lymphoma cells [205]. The cisplatin-resistant MCL cell line (JeKo-1/DDP) is also affected by KU-55933, causing an increase in cisplatin-induced DNA damage [206]. Finally, ATM inhibition by KU-55933 decreases cell viability in hairy cell leukemia (HCL) cells via inhibiting the hyperactivated NF-κB pathway in these cells [207].

A novel class of ATM inhibitors, known as AZD0156, inhibits ATM kinase activity and exerts similar effects to KU-55933 [208]. This inhibitor produces satisfactory outcomes and shows robust efficacy in murine models of AML [209]. KU-60019 (KU-55933 analog) is a potent and selective inhibitor of ATM, which has been used in the treatment of solid tumors, as well as leukemia and lymphoma [210, 211]. In this regard, KU-60019 potentiates bendamustine activity on human B cell lymphoma cell lines (BALM3, SU-DHL-4, U698M, and SKW4), lymphoblastoid cell line (BALM1), and myeloma cells (RPMI8226) [212].

Caffein can inhibit both ATM and ATR and it induces G1/S checkpoint arrest, as well as a G2/M checkpoint delay in K562 erythroblastic leukemia cells [213]. Nevertheless, similar to wortmannin, the broad nonspecific effects and high in vivo toxicity at the concentrations required to inhibit ATM, prohibit their use in the clinic [214, 215].

ATR inhibitors

Similar to ATM, ATR inhibition in murine models of MLL-rearranged AML can prevent tumor growth and also reduce the tumor burden. These outcomes have been detected in xenografts of a human AML-MLL cell line [201]. VE-821 is a selective ATR inhibitor, with more than 100-fold selectivity for ATR versus ATM [216]. In combination therapy using ATM inhibitor (KU55933), VE-821 showed an increased radiosensitizing effect in promyelocytic leukemia cell line (HL60) [217]. Similarly, a combination therapy approach, using VE-821 and KU-55933, significantly decreases the survival of MM cells while inhibition of other NHEJ components (i.e., DNA-PK), does not exert any cytotoxic effects on the viability of MM cells [218]. VE-822 (VX-970) is an improved analog of VE-821, which is more soluble, potent, and selective than VE-821 and has better pharmacodynamic properties [219]. In a murine AML model, VE-822 acts as a chemosensitizer in combination with gemcitabine and results in complete eradication of disseminated leukemia [220].

Another ATR inhibitor, AZD6738 (Ceralasertib), is under clinical development and has been approved for oral prescription. It was shown that AZD6738 was selectively cytotoxic to both TP53- and ATM-deficient CLL cell lines and primary tumor samples. Reduction in the proportion of CLL cells was also confirmed in vivo using primary xenograft models of TP53- or ATM-defective CLL. Additionally, AZD6738 sensitized primary CLL cells with such defects to chemotherapy and ibrutinib, suggesting ATR as a promising therapeutic target for TP53- or ATM-defective CLL [221]. A profound synthetic lethal interaction was reported between ATR and the ATM-p53 tumor suppressor pathway in cells treated with DNA-damaging agents [222]. Likewise, inhibition of ATR kinase activity in MCL with ATM-loss of function results in synthetic lethality, which represents ATR inhibitor as a therapeutic approach in ATM-deficient tumors [223]. As a combination therapy, AZD6738 augments carboplatin, bendamustine, and cyclophosphamide effects and reduces the tumor burden in an ATM-deficient DLBCL

mouse model [219]. A phase I clinical trial of AZD6738 in combination with acalabrutinib is under evaluation in relapsed or refractory high-risk CLL patients [ClinicalTrials.gov Identifier NCT03328273]. BAY 1895344 is also a novel selective ATR kinase inhibitor. In a panel of cancer cell lines harboring different mutations in DDR pathways, BAY 1895344 displayed potent antiproliferative activity, and MCL cell lines appeared to be the most sensitive cancer type. BAY 1895344 also exhibits a synergistic activity in combination with chemotherapy agents and external beam radiotherapy [224]. At this time, BAY 1895344 is under clinical investigation in patients with advanced solid tumors and lymphomas [ClinicalTrials.gov Identifier: NCT03188965].

Oncogenic expression of Ras and suppression of ATR synergistically increase the genomic instability in MLL-ENL-driven AML, highlighting ATR inhibition as a promising therapeutic strategy. This toxic interaction between ATR suppression and oncogenic stress occurred.

irrespective of status p53 [232]. Treatment with AZ20, another ATR-selective inhibitor, triggered proliferation inhibition in AML cell lines as well as primary patient samples. Moreover, AZ20 synergistically cooperates with cytarabine to generate DNA damage, induce apoptosis, and inhibit proliferation in AML cell lines and primary AML patient samples [233]. Palacin et al. reported that inhibition of the kinase ATR with AZ20 could induce chromosomal breakage and death in a mouse model of MLL-rearranged AML, independently of p53 [201]. Table 4 summarizes ATR and ATM inhibitors in hematologic malignancies.

Lig IV inhibition

SCR7 (an L189 derivative) was initially identified as a DNA ligase IV inhibitor. Srivastava et al. used SCR7 in various cell lines, including human leukemia cells, and found that it could significantly inhibit tumor progression [234]. However, more recent work suggests that this inhibitor is neither a selective nor a potent inhibitor of human DNA ligase IV [235]. The RNA interference strategy against Lig IV leads to significant radio sensitization in multiple cultured cell lines and murine models [172, 236].

MRN complex inhibition

The MRN complex plays two general and determinative roles in DSB repair: (1) DSB sensitivity by activation of ATM; and (2) determination of the pathway fate by MRE11 nuclease activity. Extended researches on MRE11 resulted in a class of inhibitors that selectively prevent the nuclease activities of MRE11 [237]. This study demonstrated that inhibition of endonuclease activity pushes the cell to NHEJ, and blockading the exonuclease activity causes a repair defect. These observations revealed the therapeutically potential impact of targeting the MRE11. Mirin is a molecule, which inhibits both MRN-dependent activation of ATM and MRE11 exonuclease activity [238]. In c-Myc-driven lymphoma, an increase in DNA damage, reduction of cellular survival, and a sharp increase in the apoptosis rate were seen following the inhibition of MRE11 exonuclease activity. Also, in a murine model with IgH/Myc translocation and c-Myc or N-Myc overexpression, pro-B lymphomagenesis was suppressed by mirin-induced inactivation of MRE11 exonuclease activity [239].

Conclusion and future prospects

Components of DSBR pathways are the guards of genome integrity. Defects of these components are causal factors for genomic instability, including translocations and DNA mutations which contribute to the development and progression of hematological malignancies. When cancer cells are deficient in certain DNA repair pathway, they are highly addicted to alternative repair pathways for their survival. As a result, identifying the components of these compensating pathways in different types of hematologic malignancies may provide us with potential biomarkers for predicting prognosis and guiding treatment choice. Unfaithful repair of DNA lesions coupled with the survival advantage of tumor cells may contribute to drug resistance in hematologic malignancies. Thus, the application of specific DNA repair targeted agents with DNA damage insult, such as chemotherapy or radiation is a more effective strategy for killing tumor cells.

DNA repair targeted agents are increasingly moving from lab to clinic, which positively affects the treatment opportunities in hematologic malignancies. However, the long-term effects of treatment with DNA repair inhibitors should be evaluated with caution as DNA repair inhibition can compromise genomic integrity in normal cells and potentially may develop a malignant phenotype. Furthermore, resistance to DNA repair inhibitors may be an evolving challenge. Therefore, it is crucial to develop alternative DNA repair targets. On the other hand, the important role of some trace elements [240], cellular processes such as neddylation [241], chromatin remodeling factors [242], and tumor microenvironment [243] on the success of hampering DNA repair pathways is indispensable. For instance, lymphoblasts in ALL overexpress VLA-4, which binds to osteopontin (OPN) secreted by osteoblasts in the bone marrow niche. This interaction of VLA-4 with OPN provides an opportunity for leukemic cells to enter the dormancy phase, which decreases their sensitivity to DSB inducers [244].

Development of clinically validated biomarkers of response and resistance and standard biomarker assays

Table 4 Therapeutic approaches against ATR and ATM in hematologic malignancies

Targets	Drugs	Type of malignancy	Highlights	Ref
ATM	KU-55933	Jurkat cells	Impairment of the auto-phosphorylation of ATM and inhibition of H2AX phosphorylation	[203, 225]
		MV4-11 cells (AML cell line)	ATM inhibition radiosensitized MV4-11 leukemia cells	[182]
		P39 and MOLM-13 cell lines (MDS cell lines)	ATM inhibition increase radiosensitization of MDS cells	[182]
		EBV-driven Burkitt lymphoma cells	Inhibition of EBV replication through inhibition of KAP1 phosphorylation	[205]
		Ramos cells	Prevention of ATM auto-phosphorylation and potentiation of etoposide-induced apoptosis	[226]
		Cisplatin-resistant MCL cell line (JeKo-1/DDP)	Enhanced cisplatin-induced DNA damage	[206]
		HCL cell line MLMA	Induction of apoptosis through inhibiting NF-κB pathway	[207]
	KU-59403	Jurkat cells	Showing higher potency, tissue distribution, and efficacy over KU-55933	[225]
	AZD0156	AML	exhibits therapeutic potential in a mouse model of MLL-rearranged AML	[227]
	KU-60019	Human B cell lymphoma cell lines, lymphoblastoid cell lines, and myeloma lines	KU-60019 potentiates bendamustine activity	[212]
		MCL cell lines	KU60019 synergizes the antineoplastic effect of romidepsin	[228]
	Caffeine (Inhibitor of both ATM and ATR)	K562 leukemia cells	Caffeine sensitises the cells to genotoxic modalities, particularly irradiation	[229]
		Lymphoma patients	Potentiated chemotherapy and induction of complete remission	[213]
ATR	VE-821	APL cells	Increase of radio sensitization	[217, 218]
		MM cells	Significantly increased apoptosis of MM cells in combination with KU-55933	[218]
		TP53-mutant MM cell lines	As monotherapy alone and in combination with DNA damaging agents, CX5461 or melphalan	[230]
	VE-822 (VX-970)	AML	Increase antileukemic activity of hydroxyurea and gemcitabine in AML mouse model	[220]
	AZD6738	CLL patients	ATR inhibition induces synthetic lethality in TP53- or ATM-defective CLL cells	[221]
		ATM-deficient DLBCL model	Combination therapy with carboplatin, bendamustine, and cyclophosphamide	[219]
		Relapsed/refractory high-risk CLL patients	A phase I clinical trial of AZD6738 in combination with acalabrutinib [Trial identifier: NCT03328273]	-
	BAY1895344	MCL models	Synergistic anti-tumor activity in combination with DNA damage-inducing chemotherapy or radiation therapy	[224]
	AZ20	AML-MLL murine model	Strong cytotoxic effects in vitro and in murine models, irrespective of p53 status	[231]
	WO2010/073034	ATM-deficient MCL	Promising results both in vitro and in vivo models	[223]

are necessary for the optimization of the clinical application of targeted DNA repair inhibitors. With the great advances made in cancer genomics, we gain better insight into the tumor heterogeneity from patient to patient. Personalized cancer therapy based on a repertoire of DNA repair deficiencies in patients with hematology malignancies can achieve tumor selective therapy and low-side effects. Molecular profiling of tumors will also help clinicians to adjust the dose of chemotherapy in combined-modality strategies in order to reduce the toxicity of current treatments for hematologic malignancies [245, 246].

In summary, this review indicates the potential opportunities to combine C-NHEJ and A-EJ inhibitors with chemoradiation treatment modalities for inducing synthetic lethal vulnerability in hematologic malignant cells with up-regulation of these pathways.

Abbreviations

DSB: DNA double-strand break; CSR: Class-switch recombination; HR: Homologous recombination; NHEJ: Non-homologous end-joining; C-NHEJ: Classical non-homologous end-joining; A-NHEJ or A-EJ: Alternative non-homologous end-joining pathways; AT: Ataxia-telangiectasia; DNA-PK: DNA-dependent protein kinase; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; SSA: Single-strand annealing; MMEJ: Microhomology-mediated end-joining;

MDS: Myelodysplastic syndromes; MM: Multiple myeloma; B-CLL: B cell chronic lymphocytic leukemia; PK: DNA–protein kinase; TCRs: T-cell receptors; T-ALL: T-cell ALL; T-PLL: T-cell prolymphocytic leukemia; NHL: Hodgkin lymphoma; ATL: Adult T-cell leukemia; HBZ: Leucine zipper (bZIP) factor; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma; MALT: Mucosa-associated lymphoid tissue; FCL: Follicle center lymphoma; EBV: Epstein–Barr virus; AID: Activation-induced cytidine deaminase; HSC: Hematopoietic stem cell; RAEB-1: Refractory anemia with excess blasts; t-MDS: Therapy-related MDS; MGUS: Monoclonal gammopathy of unknown significance.

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