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Review

Microhomology-mediated end joining: Good, bad and ugly

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ABSTRACT

DNA double-strand breaks (DSBs) are induced by a variety of genotoxic agents, including ionizing radiation and chemotherapy drugs for treating cancers. The elimination of DSBs proceeds via distinctive error-free and error-prone pathways. Repair by homologous recombination (HR) is largely error-free and mediated by RAD51/BRCA2 gene products. Classical non-homologous end joining (C-NHEJ) requires the Ku heterodimer and can efficiently rejoin breaks, with occasional loss or gain of DNA information. Recently, evidence has unveiled another DNA end-joining mechanism that is independent of recombination factors and Ku proteins, termed alternative non-homologous end joining (A-NHEJ). While A-NHEJ-mediated repair does not require homology, in a subtype of A-NHEJ, DSB breaks are sealed by microhomology (MH)-mediated base-pairing of DNA single strands, followed by nucleolytic trimming of DNA flaps, DNA gap filling, and DNA ligation, yielding products that are always associated with DNA deletion. This highly error-prone DSB repair pathway is termed microhomology-mediated end joining (MMEJ). Dissecting the mechanisms of MMEJ is of great interest because of its potential to destabilize the genome through gene deletions and chromosomal rearrangements in cells deficient in canonical repair pathways, including HR and C-NHEJ. In addition, evidence now suggests that MMEJ plays a physiological role in normal cells.

1. Introduction

Cellular DNA double-strand breaks (DSBs) arise from endogenous damage sources, such as replication errors, reactive oxygen species, and enzymatic processes, as well as exogenous damage sources, such as ionizing radiation and chemotherapeutic agents [1]. DSBs are arguably the most toxic DNA lesions, because if not repaired, a single DSB can kill a cell. Moreover, if a DSB is repaired improperly, it can induce gross chromosomal rearrangements and mutagenesis, which are the most common drivers underlying oncogenesis and a host of genetic diseases [2–5]. Cells have developed multiple mechanisms to quickly and accurately fix broken DNA − thus restoring chromosomal integrity − including homologous recombination, and classical and alternative non-homologous end joining (C-NHEJ and A-NHEJ, respectively).

In homologous recombination (HR), the break repair is directed by an intact homologous sequence, usually from sister chromatids, following DNA replication [6–9]. Four types of HR have been described: gene conversion, synthesis-dependent strand annealing (SDSA), break-induced replication (BIR), and single-strand annealing (SSA). All but SSA are dependent on the *RAD51* gene, and they all initiate repair with the resection of DSB ends by a 5′-to-3′ exonuclease to produce long 3′-ended, single-stranded DNA (ssDNA) tails [10]. In gene conversion, SDSA, and BIR, the ssDNA invades the homologous donor sequence to prime repair DNA synthesis. In SSA, the complementary strands of the homologous regions flanking a DSB anneal, producing an intermediate with two non-homologous 3′-ended tails that must be removed for new DNA synthesis and ligation to occur [11,12].

Alternatively, classical non-homologous end joining (C-NHEJ) repairs DSBs by juxtaposing and ligating DNA ends, using very little (1–4 nucleotides [nt]) or no complementary base pairing [1,13–15]. This can occur throughout the cell cycle; however, it is most active in G1 [16–18]. In C-NHEJ in mammalian cells, the Ku70/Ku80 heterodimer first binds to DSB ends and recruits other NHEJ factors, including DNA-dependent protein kinase catalytic subunit (DNA-PKcs), X-ray repair cross complementing 4 (XRCC4), DNA ligase 4 (LIG4), and XRCC4-like factor (XLF), to catalyze DNA ligation across the DNA breaks [19–22]. If the DNA ends are not compatible for ligation, then DNA-end processing, such as trimming, filling-in, or blocking-end removal, ensues by one of many processing enzymes, such as Artemis, polynucleotide kinase 3′-phosphatase (PNKP), aprataxin (APTX) and PNKP-like factor (APLF),

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DNA polymerase mu (Polμ), DNA polymerase lambda (Polλ), or Werner syndrome RecQ-like helicase (WRN), prior to ligation [23–27].

Finally, alternative NHEJ (A-NHEJ), which includes microhomology (MH)-mediated end joining (MMEJ), repairs DNA DSBs by annealing 2–20-bp stretches of overlapping bases flanking the DSB [28–31]. Not all A-NHEJ produces repair junctions with MH; therefore, MMEJ likely only corresponds to a subset of A-NHEJ. Genetically, MMEJ does not require Ku70/Ku80, RAD51, BRCA2, or LIG4, but both processes require the MRE11-RAD50-NBS1 complex [MRN complex; Mre11-Rad50-Xrs2 (MRX) complex in yeast], DNA polymerase theta (Polθ) or the B and X family polymerases in yeast (Polδ and Pol4), CtBP-interacting protein (CtIP, Sae2 in yeast), poly (ADP-ribose) polymerase 1 (PARP1), ataxia telangiectasia mutated (ATM; Tel1 in yeast), and flap endonuclease 1 (FEN1) [32–40]. In this review, we will focus on the role of MMEJ as a genome destabilizer, and we will show that, despite the high mutation burden associated with MMEJ, it provides valuable physiological functions. We will also describe the pathological role of MMEJ as a back-up repair pathway, and we will discuss the emerging possibility that MMEJ is an attractive anti-cancer drug target.

2. Biochemical steps of MMEJ

Before we evaluate the current model of MMEJ, and the associated molecular and biochemical steps, we would like to highlight several recent, outstanding reviews on MMEJ. We encourage readers to refer to these reviews for additional, in-depth information about the components and attributes of MMEJ [28–31]. Throughout this review, we will primarily use the terminology for mammalian MMEJ factors, but we will list their yeast counterparts in parentheses. If the genes or proteins only exist in yeast, or in organisms other than mammals, we will designate their origin using small letters in front of their name (e.g. ySrs2; Srs2 protein in yeast).

Operationally, MMEJ can be subdivided into three discrete steps: pre-annealing, annealing, and post-annealing of the flanking MHs (Fig. 1). The first step in MMEJ involves end resection to expose the flanking MHs for annealing. Resection likely operates via a common mechanism between HR and MMEJ; the MRN complex (MRX in budding yeast) along with CtIP (Sae2 in yeast), introduces a nick near the DSB lesion and degrades DNA using 3′-5′ exonuclease activity [38,41–43]. More extensive 5′-3′ resection is catalyzed by the Bloom syndrome RecQ-like helicase (BLM)/exonuclease 1 (EXO1) (Sgs1/Exo1 and Dna2 in budding yeast) [38,44–46]. Interestingly, BLM/EXO1 is not only dispensable for MMEJ, but it also suppresses MMEJ when MHs are located within 2-kb of the DSBs [38,47]. Thus, extensive resection might favor HR over MMEJ.

Once exposed by resection, the flanking MHs will anneal via an unidentified mechanism. The size of the MHs, engaged in annealing, likely dictates the stability of the annealed intermediates and the repair outcome. Consistent with this idea, GC-rich MHs facilitate MMEJ *in vitro* [48], whereas mismatched nucleotides within MHs reduce MMEJ [49]. Finally, the ssDNA-binding, heterotrimeric replication protein A (RPA) complex, which consists of RPA70, RPA32, and RPA14, interferes with MMEJ mainly by preventing annealing of ssDNA [47,50].

The annealed intermediates are further modified by the XPF/ERCC1 (Rad1/Rad10 in yeast) structure-specific nuclease complex, which trims the non-homologous tails and produces 3′-hydroxyl termini that are eligible for extension by DNA polymerase [36,51]. The low fidelity DNA polymerase Polθ [52], which is encoded by *POLQ*, is capable of extending mismatched termini, ssDNA, and partial ssDNA [53]. Polθ and its fly ortholog *dm*Mus308 have been implicated in MMEJ of eroded telomeres and DSBs induced by stressed replication forks [32,33,54,55]. In budding yeast, there is no Polθ homologue; instead, polymerase delta (Polδ) and Pol4 are important for yeast MMEJ [56,57].

Finally, the DNA ligation is catalyzed redundantly by LIG3 and LIG1, or partially by Dnl4 in yeast [36,58–60]. In mammals, MMEJ also requires X-ray repair cross complementing 1 (XRCC1) and PARP1. XRCC1/LIG3 and PARP1 have been implicated in end modification/synapsis and in recruitment of Polθ to DSB lesions to prime MMEJ [33]. Notably, the reported genetic requirements of MMEJ are surprisingly diverse and significantly divergent across species. Therefore, the ligases involved in MMEJ or the role of XRCC1 in MMEJ remain controversial [60]. Although additional studies are surely needed to resolve these discrepancies, one possible reason for these reported differences might stem from the fact that MMEJ and A-NHEJ are not necessarily part of a single pathway. Instead, MMEJ and A-NHEJ comprise several different mechanisms, each with their own genetic requirements. Adding to this complexity, another end-joining pathway, was described recently; this pathway has more resemblance to C-NHEJ and operates at G1 upon limited resection [61]. In the future, it will be necessary to reassess the precise factors involved in each of these processes and their relationship to each other.

3. Genomic consequences of MMEJ

Although DSB repair pathways provide cells the capacity to avoid the more catastrophic consequences that follow repair failure, the DSB repair pathways are often mutagenic and are the primary source of gross chromosomal rearrangements and chromosomal instability upon DNA damage (Fig. 2). HR, which is regarded as the high-fidelity repair pathway, can trigger chromosomal translocations if the recombination intermediates are resolved by crossover between allelic or non-homologous chromosomes [62]. BIR and SSA can also produce sequence deletions and non-reciprocal translocations at sequences flanking the breakpoint junctions [40,63]. C-NHEJ leads to small sequence insertions or deletions (indels) at the breakpoint junction due to the end processing that occurs prior to ligation by different nucleases and polymerases [64–67]. Moreover, if more than two breaks occur simultaneously, improper joining of these DSBs by C-NHEJ can also produce chromosomal translocations and rearrangements [68].

However, among the DSB repair pathways, MMEJ appears to play a major role in DSB-induced mutagenesis. MMEJ is always mutagenic because one of the two MH regions, and the inter-MH region, will be deleted from the repair product. Analysis of ~7000 deletion breakpoints in the *C. elegans* revealed that the majority of ethyl methane sulfonate (EMS) or photoactivated trimethylpsolaren (UV/TMP)-induced indels are products of Polθ-mediated end joining [69]. These breakpoint junctions often contain short, sometimes templated, or non-templated, insertions that are reminiscent of the breakpoint junctions of complex copy number variants, which often contain MHs and are associated with a high frequency of missense and indel mutations in the flanking DNA due to error-prone repair synthesis [69]. The terminal transferase activity and frequent template switching of Polθ, followed by the iterative synthesis of ssDNA or partial ssDNA, might account for frequent sequence insertions at the breakpoint junctions [70]. Mammalian Polθ also has RAD51-binding domains that can block RAD51-mediated recombination and thereby promote end joining pathways including MMEJ [71].

MMEJ has also been implicated in the formation of chromosomal translocations and gross chromosomal rearrangements in mouse, which could explain why most breakpoints from chromosomal translocations in human somatic cells and cancers feature MHs at the junctions [72,73]. In yeast, it was initially shown that, if multiple breaks form simultaneously, MMEJ mediates promiscuous end joining, leading to chromosomal translocations and rearrangements [49]. To further test the role of MMEJ in the formation of chromosomal translocation, two DSBs were induced on different chromosomes, using CRISPR-CAS9 or I-SceI nucleases, in murine and human cells deficient in C-NHEJ, and the frequencies of reciprocal translocation induction were measured [74,75]. They found that, in mouse embryonic stem cells, inactivation of the NHEJ factor XRCC4 elevates chromosomal rearrangements approximately 5-fold over those in controls, and over 60% of the XRCC4-

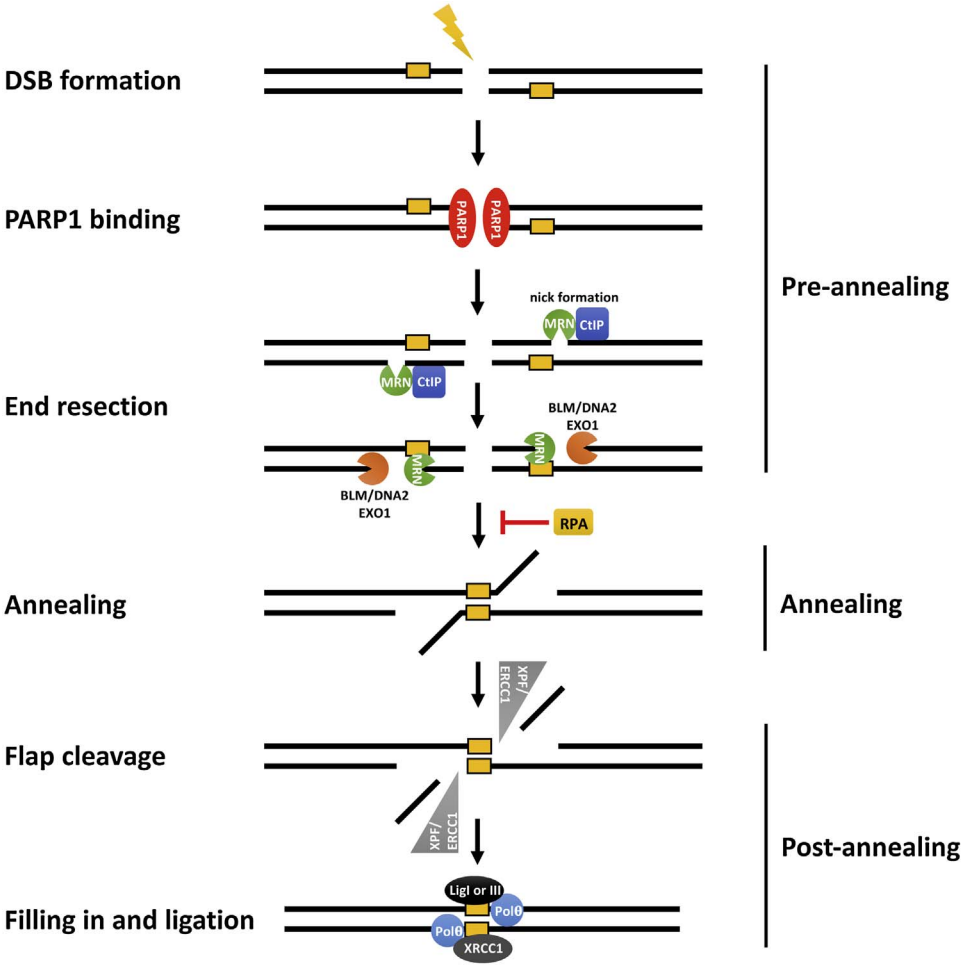

Fig. 1. The basic mechanisms of MMEJ in human cells. MMEJ could be divided to three discrete steps, pre-annealing, annealing, and post-annealing of the flanking MHs. PARP1 binds to DSB ends and facilitates the recruitment of resection factors [CtIP and Mre11 complex (Mre11/Rad50/Nbs1)] to uncover MHs (shown in yellow boxes) flanking DSBs. MHs that are far from the break likely require extensive resection by BLM/EXO1 to facilitate MMEJ. Annealing of MHs, which is inhibited by single strand binding RPA complex, induces the formation of non-homologous tails/flaps. Non-homologous tails/flaps are then removed by XPF/ERCC1 nuclease before filling-in synthesis and ligation by Polθ and LigI/III, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

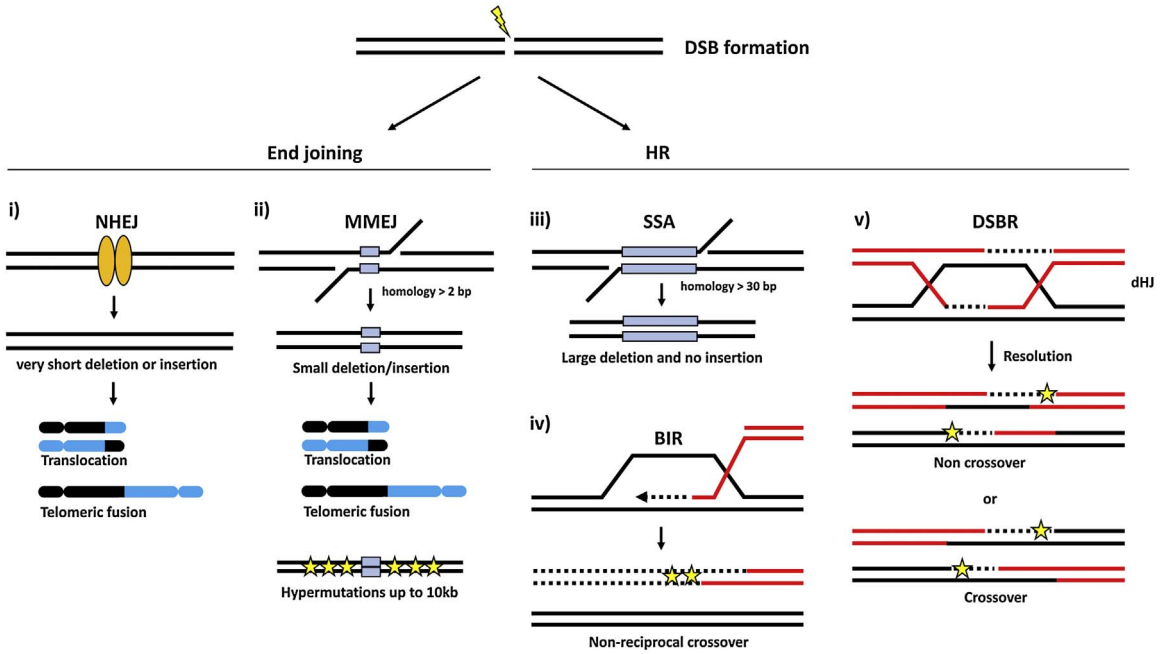

Fig. 2. Genomic instability caused by DNA DSB repair mechanisms. C-NHEJ (**i**) generates small sequence deletions/insertions at breakpoint junctions. MMEJ (**ii**) induces deletions and insertions at the breakpoint junctions and hypermutagenesis at the flanking DNA sequence up to several kilobases from the break. Both C-NHEJ and MMEJ could trigger chromosomal translocations and telomeric fusions. SSA (**iii**) also induces large deletions but not insertions at repair junctions. In BIR (**iv**) and gene conversion (**v**), low fidelity DNA synthesis produces mutagenesis at the flanking DNA sequence and could induce chromosomal translocations if recombination involves non-allelic template and/or crossover formation. Blue boxes represent homologies and the stars represent mutations. The dotted lines are newly synthesized DNA. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

depletion-driven translocations contain 1–4-bp MHs [74,75]. Moreover, in murine cells, the formation of chromosomal aberrations is dependent on the MMEJ repair factors CtIP and LIG3 [60,76]. However, in human cells, the formation of chromosomal translocations is not dependent on MMEJ factors but is dependent on C-NHEJ factors, including Ligase IV [74]. Recently, a unique variant of NHEJ, termed resection-dependent NHEJ (*rd*NHEJ), has been described [61]; this variant operates with delayed kinetics and repair of DNA ends that are resected by CtIP or Artemis in the G1 phase of the cell cycle. These repair events are distinct from MMEJ because they do not depend on PARP1 and LIG3 but do depend on DNA-PKcs, and Ligase IV. Thus, it has been suggested that *rd*NHEJ, rather than A-NHEJ, induces chromosomal translocation formation in human cells [61]. Alternatively, the human cell lines used for this study could be deficient in MRN/ATM function [77] and this may have influenced the contribution of A-NHEJ to the rearrangements [78].

In addition to chromosomal structural changes, MMEJ-mediated DSB repair elevates the mutation frequency at breakpoint junctions, which is likely due to the use of low fidelity polymerases in repair synthesis and/or to the formation of mutation-prone ssDNA. Indeed, hypermutagenesis frequently occurs in the sequences flanking the breakpoint junctions, which has been suggested to be due to the error-prone nature of Polθ [55]. However, in yeast, which lacks a Polθ homologue, hypermutagenesis still occurs within sequences flanking the breakpoint junctions, and this hypermutagenesis extends 7–9 kb from the junctions [79]. These data suggest that the hypermutagenesis is not solely due to Polθ; instead, it is an inherent feature of MMEJ. It is possible that the hypermutagenesis is due to the slow kinetics of MMEJ [79], inevitably leading to the formation of extensive ssDNA, which is more prone to irreversible sequence changes upon exogenous and endogenous DNA damage [80]. Interestingly, the junctions from chromosomal rearrangements and copy number variants (CNVs) are often associated with increased mutagenesis within several kilobases flanking the breakpoints, and most of these junctions harbor MHs at the breakpoints, likely resulting from MMEJ or micro-BIR [81–85].

4. Pathological functions of MMEJ and its potential as an anti-cancer drug target

Because of the high mutation burden and chromosome structural changes that accompany MMEJ, one would assume that MMEJ is tightly regulated, and that it would not be the first option for repairing DSBs. Indeed, accumulating evidence suggests that, when C-NHEJ or HR are deficient, MMEJ is a surprisingly robust and efficient alternative repair option.

Multiple lines of evidence suggest that MMEJ is efficient when C-NHEJ is deficient. For instance, immunoglobulin class-switch DNA recombination (CSR) [86], initiated by activation-induced cytidine deaminase (AID)-introduced DSBs in the switch (S) regions, typically involves Ku70/Ku86-mediated NHEJ [87,88]. However, in Ku-deficient B cells, MMEJ still promotes CSR, albeit at a reduced level compared with that of NHEJ, introducing MHs at the S–S junctions [86–90].

Moreover, uncapped telomere fusion can be catalyzed in a C-NHEJ- or MMEJ-dependent manner. Eukaryotic telomeres are protected by the Shelterin complex, which contains TRF1, TRF2, POT1, RAP1, TIN2, and TPP1 [91]. In murine cells, TRF2 deficiency induces checkpoint sensor 53BP1-dependent, C-NHEJ-mediated telomere fusion [92]. However, in *53BP1*$^{-/-}$ or *Lig4*$^{-/-}$ murine cells with a TPP1-POT1 deficiency, telomere fusions are still induced under naturally shortened telomere environments, presumably via an A-NHEJ pathway [92]. Importantly, in human cells, sequencing analysis data showed that shortened telomere fusion is due to MMEJ, and not C-NHEJ [93]. Confusingly, however, subsequent work demonstrated that both LIG3 and LIG4 play roles in telomere fusions in human cells [94].

MMEJ provides a back-up DNA repair mechanism upon HR deficiency, particularly in cancer cells [50,71]. A recent study showed that BRCA2-deficient ovarian cancer cells express high levels of *POLQ*, which may contribute to elevated MMEJ in these cells [71]. Therefore, inhibition of Polθ sensitizes these cells to genotoxic chemicals and PARP1 inhibitor treatment, indicating Polθ inhibition as a novel cancer therapeutic strategy. Cancer cells with *BRCA1* or *BRCA2* mutations are sensitive to PARP1 inhibitor treatment [95–97]; however, the treated cells eventually develop PARP1 resistance as a result of a secondary BRCA mutation, depletion of 53BP1, downregulation of PARP1, or upregulation of ABC transporters (see review in [98]). To overcome PARP1 inhibitor resistance, several studies have investigated the effects of co-treatment with PARP1 inhibitors and histone deacetylase (HDAC) inhibitors [99–103]. Evidence suggests that HDAC inhibitors decrease the expression of HR factors [103–105]. Interestingly, the deacetylase and mono-ADP-transferase SIRT6 deacetylates the MMEJ factor CtIP, which stimulates CtIP activity. SIRT6 could thus increase MMEJ activity and be a potential therapeutic target in HR-deficient cancer cells with high MMEJ activity.

There are also reports of a concomitant upregulation of MMEJ, and downregulation of C-NHEJ activity in certain cancer cells. For instance, the reciprocal translocation t(9;22)(q34;q11) results in expression of the oncogenic BCR/ABL fusion gene that causes chronic myeloid leukemia (CML). Interestingly, levels of the MMEJ factors WRN and LIG3 are increased, whereas the C-NHEJ factors Artemis and LIG4 are decreased, in CML cells [106]. Moreover, siRNA-mediated inactivation of WRN and LIG3 decreases end-joining efficiency and leads to persistent DSBs in CML cells [106]. In human bladder cancer, the levels of C-NHEJ factors are also reduced, suggesting that these cancer cells may also rely on MMEJ to repair their DSBs [107]. This increased use of the MMEJ pathway in specific cancer cells has important implications for cancer therapy.

5. Physiological role of MMEJ

Although ample evidence supports the role of MMEJ as the back-up pathway for cells deficient in C-NHEJ and HR, the physiological roles of MMEJ in cells proficient in C-NHEJ and HR are not well understood and remain debatable. Unlike DSBs induced by site-specific nucleases in experimental settings, radiation generates DSBs with complex end termini such as 3′-phosphate (P) and 3′-phosphoglycolate [108]. Prior to ligation, the 3′-Ps at DNA ends must be removed by PNKP [109], and blocking 3′-P removal at DSBs increases MMEJ approximately 3-fold in cancer cells [110]. This result suggests the intriguing possibility that intracellular DSBs, induced by radiation or physiological agents, are more dependent on MMEJ for repair. Furthermore, recent evidence suggests that mammalian mitochondrial extract relies on CtIP, FEN1, LIG3, MRE11, and PARP1, but not LIG4, to repair DSBs [111]. Notably, more than 85% of over 100 types of mitochondrial (mt) DNA deletions are flanked by short repeated sequences, suggesting that error-prone MMEJ in mtDNA may be associated with human mitochondrial disorders [112–114]. However, it should be noted that the reliance of DSB repair in mitochondria on MMEJ can − at least in part − be attributed to the fact that LIG3 is the sole ligase expressed in that organelle. Overall, the emerging theme is that if DSB breaks are not repaired quickly, then they are more likely to be the substrate of MMEJ for repair.

Alternatively, it may be that MMEJ is favored for DSB repair over other DNA repair pathways under specific conditions. Indeed, several regulatory mechanisms that favor MMEJ have been reported recently. For instance, S-phase phosphorylation of CtIP triggers MMEJ [38,115]. Moreover, deacetylation of CtIP by SIRT6 could activate CtIP resection activity and increase MMEJ [116]. In cells in G1, 53BP1 also promotes MMEJ [117], and interestingly, knockdown of *53BP1* decreases distal MMEJ (> 1000 bp distance from DSB) but not proximal MMEJ [117]. Lastly, evidence suggests that Polθ-dependent MMEJ operates primarily in S phase. One study used a reporter system with MHs flanking I-SceI-induced DSB breaks to illustrate the predominance of MMEJ in S/G2

[38]. It is possible that NHEJ and HR are both suppressed in the S phase, rendering MMEJ the sole option to repair DSBs arising during replication collapse and stress. Furthermore, because MMEJ is inhibited by extensive resection, MMEJ may be optimal under limited resection conditions; however, the physiological conditions that favor partial resection are unknown.

6. Concluding remarks

MMEJ is an emerging drug target due to its role as the back-up DSB repair pathway in C-NHEJ- or HR-deficient cancers [71,118–120]. However, accumulating evidence suggests that MMEJ is not simply a back-up for HR and C-NHEJ. MMEJ likely has bona-fide, physiological roles in DSB repair in many eukaryotic cells. Moreover, we would like to emphasize that, although MMEJ is highly destabilizing and capable of triggering chromosomal translocations and rearrangements, inactivation of the MMEJ factor Polθ results in vast chromosomal deletions and instability [34,54,121], indicating that MMEJ also provides necessary protective functions to the genome. All these results warrant more systematic and extensive analyses of the biochemical and genetic components of MMEJ in multiple models. The outcome of such studies will further elucidate the intricate network and regulation of DSB repair in human cells, thereby facilitating the development of novel therapeutic strategies to eliminate cancer cells with little or no side effects.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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