Double-Strand Break Repair

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Synopsis

DNA double-strand breaks (DSBs) are the most dangerous form of DNA damage and can lead to death, mutation, or malignant transformation. Mammalian cells use three major pathways to repair DSBs: homologous recombination (HR), classical nonhomologous end joining (C-NHEJ), and alternative end joining (A-NHEJ). Cells choose among the pathways by interactions of the pathways with CtIP and 53BP1.

HR is restricted to S and G2 phases of the cell cycle, utilizing homologous newly replicated DNA for error-free repair. Inherited mutations in the HR genes BRCA1, BRCA2, and PALB2 cause susceptibility to breast, ovarian, and pancreatic cancer. C-NHEJ operates during all phases of the cell cycle and during V(D)J recombination of the antibody and T-cell receptor genes, joining DNA ends while minimizing nucleotide loss and addition for error-prone repair. Inherited mutations in the C-NHEJ genes DNA-PKcs, Artemis, and XLF cause the syndrome of radiation sensitivity with severe combined immunodeficiency. A-NHEJ is a backup pathway for C-NHEJ, joining DNA ends after resection back to regions of microhomology for error-prone repair. A-NHEJ is responsible for creating the chromosomal translocations seen in cancer. Thus, understanding DSB repair pathways will lead to insights for immunology and cancer.

Introduction

DNA double-strand breaks (DSBs) pose grave problems for the mammalian cell. Unrepaired breaks lead to death. Inaccurate repair generates mutations or chromosome translocations, which can lead to cancer.

DSBs arise from many sources. Exogenous sources include ionizing radiation and topoisomerase II inhibitors. Ionizing radiation produces ends with non-ligatable nucleotides containing ruptured ribose rings or aberrant chemical groups, such as 5'-hydroxyl, 3'-phosphate, or 3'-phosphoglycolate groups. The damaged nucleotide must be either repaired or removed prior to ligation. Topoisomerase II inhibitors include the anticancer drugs etoposide and doxorubicin. Topoisomerase II untangles newly replicated DNA by cutting both strands of one DNA double helix to allow a second DNA double helix to pass through. Topoisomerase II inhibitors trap the enzyme as a protein-bridged DSB intermediate.

Endogenous sources of DSBs include V(D)J recombination and class switch recombination. V(D)J recombination generates DSBs with blunt ends and unusual hairpin ends in order to create a diverse repertoire of B-cell antibodies and T-cell receptors that recognize foreign antigens. The brief definition entitled “▶ V(D)J Recombination” provides additional information. Class switch recombination switches the constant region of an antibody while preserving its variable region. After class

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switching, the antibody recognizes the same antigen but interacts with a different effector molecule to activate a specific immunological response.

Befitting the danger of DSBs, eukaryotic cells have evolved three repair pathways (Fig. 1). Homologous recombination (HR) occurs during S and G2 phases of the cell cycle, utilizing homologous DNA (usually from the newly replicated sister chromosome) to repair DSBs. HR is a conservative repair pathway because it restores the DNA sequence even if the source of the DSB disrupts nucleotides near the ends. Classical nonhomologous end joining (C-NHEJ) joins compatible DNA ends precisely and noncompatible DNA ends with limited nucleotide deletion or addition. C-NHEJ is nonconservative but optimizes the preservation of DNA sequence. Alternative nonhomologous end joining (A-NHEJ) repairs DSBs by deleting nucleotides back to regions of microhomology, creating junctions with deletions generally larger than those from C-NHEJ. Thus, A-NHEJ is the least conservative pathway.

Prokaryotes and eukaryotes differ significantly in how they perform DSB repair. However, the eukaryotic DSB repair pathways are conserved from yeast to mammals. This review emphasizes the mammalian pathways and highlights their relevance for human disease.

Choice of the Pathway for Repairing DSBs

Choice of the repair pathway can depend on the source and timing of the DSB. V(D)J recombination generates two DSBs and funnels their joining toward C-NHEJ (Dudley et al. 2005). Class switch recombination generates two DSBs that are joined by both C-NHEJ and A-NHEJ (Yan et al. 2007). In S and G2 phases of the cell cycle, cyclin-dependent kinase CDK2 directs DSBs toward repair by HR.

MRN (Mre11-Rad50-Nbs1) accumulates rapidly at sites of DSBs, holding the two DNA ends together (Fig. 2) (Stracker and Petrini 2011). Consistent with its role in tethering DNA ends, MRN has an overall stoichiometry of Mre11$_2$-Rad50$_2$-Nbs1$_2$. The proteins in the MRN complex have distinct biochemical activities. Rad50 contains a globular domain and an extended coiled-coil ending in a hook domain that facilitates homodimerization of two Rad50 molecules. Since Rad50 interacts with Mre11 and Nbs1, Rad50 homodimerization generates the full MRN complex. Mre11 can tether two DNA ends to each other and has endonuclease and 3’–5’ exonuclease activities.

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**Fig. 1 Pathways for DSB repair.** Homologous recombination (HR) utilizes homologous DNA (red) to conserve DNA sequence. Classical nonhomologous end joining (C-NHEJ) minimizes loss of DNA in DNA sequence (black). Alternative NHEJ (A-NHEJ) deletes nucleotides back to regions of microhomology, leaving one copy of the microhomology region (black box)
in vitro. The exonuclease activity appears paradoxical, since the search for homologous sequence during HR requires DNA with a 3' overhang. Indeed, other nucleases catalyze bulk 5'–3' resection, as described below.

After binding to DNA ends at the DSB, MRN recruits ATM (ataxia telangiectasia mutated), a serine-threonine protein kinase (Stracker and Petrini 2011). ATM kinase phosphorylates a number of target proteins, leading to induction of cell cycle checkpoints, chromatin remodeling, and activation of DNA repair.

Mutations in the genes encoding the MRN and ATM proteins cause a group of related human diseases, consistent with their interaction with each other. ATM mutations cause ataxia telangiectasia (Savitsky et al. 1995), an autosomal recessive disorder characterized by poor coordination (ataxia), dilation of small blood vessels (telangiectasia), cellular sensitivity to ionizing radiation, immunodeficiency, and high risk for lymphoma and leukemia. Hypomorphic (partially inactivating) recessive mutations in Mre11 cause ataxia telangiectasia-like disorder (ATLD) (Stewart et al. 1999), manifesting ataxia and radiation sensitivity, but distinguished from ataxia telangiectasia by normal immunity, normal cancer risk, slower disease progression, and absence of telangiectasias. Hypomorphic Nbs1 mutations cause Nijmegen breakage syndrome (NBS) (Carney et al. 1998; Varon et al. 1998), which is characterized by ▶ microcephaly, facial abnormalities, short stature, ▶ immunodeficiency, radiation sensitivity, and high risk for lymphoma.

CtIP (CtBP [carboxy-terminal-binding protein]-interacting protein) was originally identified as a cofactor for the transcriptional repressor CtBP (You and Bailis 2010). Activation of the ATM kinase permits CtIP recruitment to DSBs where it interacts with the Nbs1 component of MRN. The interaction between CtIP and MRN facilitates repair by either A-NHEJ or HR (Fig. 2). CtIP undergoes phosphorylation by CDK2 during S and G2 phases of the cell cycle, channeling the DSB toward repair by HR.
The p53-binding protein 1 (53BP1) also affects the choice of repair pathway (Panier and Boulton 2014). DSBs activate the ATM signaling cascade, which leads to the phosphorylation of histone 2A variant H2AX together with the recruitment of 53BP1 to the damaged chromatin. Binding of 53BP1 to damaged chromatin blocks end resection at DSBs, preserving the DNA ends for binding by Ku and thus channeling repair toward C-NHEJ. Table 1 summarizes the proteins involved in choosing the DSB repair pathway.

### Homologous Recombination (HR)

Table 2 summarizes the HR proteins. The MRN/CtIP complex resects DNA ends, including ends with covalent modifications or bulky adducts (Buis et al. 2008; Sartori et al. 2007). MRN/CtIP resects no more than 50–110 nucleotides in the 3′–5′ direction, and this nuclease activity is dispensable for unblocked DNA ends. However, ATM-mediated phosphorylation of CtIP together with BRCA1 (breast cancer susceptibility type 1)-mediated ubiquitination of CtIP leads to the extended 5′–3′ resection of 100–200 nucleotides to form the 3′ overhang required for homology
searching during HR (San Filippo et al. 2008). Extended resection requires MRN, RPA (replication protein A), the nucleases Exo1 and DNA2, and the helicase BLM (Bloom’s syndrome protein) (Nimonkar et al. 2011).

Bloom’s syndrome is an autosomal disorder characterized by short stature, rash upon sun exposure, and a high risk for cancer, including leukemia, lymphoma, and carcinoma. Bloom’s syndrome cells show a strikingly elevated frequency of exchange events between homologous chromosomes (sister chromatid exchanges).

Neither Exo1 nor DNA2 can generate the extensive 3′ overhang required for HR when acting as a purified protein in isolation. Exo1 has a relatively weak 5′–3′ exonuclease activity. DNA2 has endonuclease activity that will degrade either a 5′ or 3′ end. However, each nuclease forms a complex with partner proteins to form an independent resection machine: BLM-DNA2-RPA-MRN or Exo1-BLM-RPA-MRN (Nimonkar et al. 2011).

In the DNA2-dependent resection machine, DNA2 and BLM act together, utilizing the helicase activity of BLM to enhance the endonuclease activity of DNA2 (Fig. 3). RPA, which binds to ssDNA, enforces 5′ polarity. In the Exo1-dependent resection machine, BLM and MRN increase the affinity of Exo1 for DNA ends. MRN and RPA increase the processivity of Exo1 resection.

![Fig. 3 Model for HR](image)

**Fig. 3 Model for HR.** During S and G2, CDK2 phosphorylates CtIP. BRCA1 then binds and ubiquitinates CtIP. The DNA ends undergo extended 5′–3′ resection catalyzed by BLM-DNA2-RPA-MRN or Exo1-BLM-RPA-MRN. Resection generates 3′ ssDNA tails of 100–200 nucleotides, which are protected by RPA binding. BRCA1 recruits PALB2 and BRCA2, which load Rad51 onto the ssDNA, displacing RPA to form a Rad51 nucleoprotein filament. Rad51 mediates strand exchange, forming a D-loop (named for the shape of the DNA structure). Strand exchange creates a primer for DNA synthesis on the homologous DNA template. The homology-guided reaction restores the broken DNA to its original sequence.
In both resection machines, RPA prevents the ssDNA from folding over and hybridizing to itself to form secondary structures. The intrinsic Mre11 nuclease activity of MRN is not required for either machine. Rather, MRN provides a scaffolding function to recruit and stimulate the nuclease activities of Exo1 and DNA2.

Both resection machines create DNA ends with 3' ssDNA overhangs of 100–200 nucleotides coated with RPA. It is not clear why HR utilizes two different resection machines, particularly because both machines include BLM, MRN, and RPA. However, the different activities of Exo1 and DNA2 as isolated nucleases raise the possibility that they have distinct functions other than simple end resection. For example, the endonuclease activity of DNA2 may allow removal of blocked 5' ends.

Following resection, several proteins cooperate to create a nucleoprotein filament that allows the ssDNA to invade homologous DNA. BRCA1 and BRCA2 (breast cancer susceptibility type 2) play key roles in loading Rad51 onto the ssDNA (Fig. 3). CDK2-mediated phosphorylation of Ser327 in CtIP facilitates its binding to BRCA1, forming a ternary complex of CtIP, MRN, and BRCA1 (Chen et al. 2008).

BRCA1 recruits BRCA2 to the DSB by binding to PALB2 (partner and nuclear localizer of BRCA2), which in turn binds to BRCA2 (Sy et al. 2009; Zhang et al. 2009). Together with DSS1 (deleted in split-hand/split-foot syndrome), BRCA2 binds to DNA via two DNA-binding domains (Yang et al. 2002). One domain binds to ssDNA and the other binds to double-stranded DNA, positioning BRCA2 at the transition point from double-stranded DNA to the 3’ ssDNA overhang. Inherited mutations in BRCA1, BRCA2, and PALB2 confer susceptibility to breast, ovarian, and prostate cancer (see the brief definition “► Hereditary Breast and Ovarian Cancer and Poly(ADP-Ribose) Polymerase Inhibition”).

BRCA2 and PALB2 load Rad51 onto the ssDNA, displacing RPA (Fig. 3). Rad51 exists as a heptamer in solution but upon binding to ssDNA forms a nucleoprotein filament with six Rad51 monomers per helical turn (San Filippo et al. 2008). Rad51 has an ATPase activity that permits turnover via dissociation from the DNA.

Rad51 is the recombinase that mediates strand exchange for HR. The nucleoprotein filament of Rad51-coated ssDNA captures a double-stranded DNA molecule and searches for homologous sequence (Fig. 3). BRCA2 and PALB2 act synergistically to stimulate Rad51-mediated strand exchange and D-loop formation (Buisson et al. 2010; Dray et al. 2010). The invading 3' end of the ssDNA primes DNA synthesis from the homologous DNA molecule, replacing DNA sequence lost from the broken DNA molecule.

The HR pathway can also lead to the crossing-over between homologous DNA chromosomes. Thus, HR-directed repair of a DSB during mitosis can lead to a detrimental loss of heterozygosity. In addition to its role in resection, BLM forms a complex with topoisomerase IIIa to suppress crossing-over during homologous recombination (Wu and Hickson 2003). This role may explain why Bloom’s syndrome cells have a high rate of sister chromatid exchange.

### Classical Nonhomologous End Joining (C-NHEJ)

C-NHEJ repairs DSBs in all phases of the cell cycle by joining the broken ends directly without using homologous DNA. DSBs may create ends with damaged nucleotides, which must be removed before ligation can occur. Since C-NHEJ lacks a mechanism for replacing the damaged nucleotides, the reaction is nonconservative. Table 3 summarizes the proteins involved in C-NHEJ.
Initiation of C-NHEJ occurs when Ku (a heterodimer of Ku70 and Ku80) binds to the DNA ends (Smider et al. 1994; Taccioli et al. 1994). Ku recruits DNA-PKcs (DNA-dependent protein kinase catalytic subunit) to the DNA end, sliding to an inward position on the DNA (Yoo and Dynan 1999). DNA-PKcs is an unusual serine-threonine protein kinase that undergoes activation on binding to DNA (Jackson et al. 1990). Activation requires free DNA ends and may involve threading of unpaired single strands into enclosed cavities in the DNA-PKcs structure (Hammarsten et al. 2000; Leuther et al. 1999) and occurs upon formation of a synaptic complex containing two DNA ends and two DNA-PKcs molecules (DeFazio et al. 2002). Subsequent DNA-PKcs autophosphorylation generates conformational changes that dissociate DNA-PKcs from the DNA ends (Chan and Lees-Miller 1996; Meek et al. 2008), which allows other C-NHEJ proteins to bind and process the DNA ends.

Three proteins participate in the ligation reaction: XRCC4 (X-ray cross-complementing protein 4), ligase IV, and XLF (XRCC-like factor). XRCC4 and ligase IV form a complex with DNA ligase activity (Grawunder et al. 1997). XLF (also known as Cernunnos) interacts with XRCC4 (Ahnesorg et al. 2006; Buck et al. 2006). XRCC4 and XLF are homodimers that interact with each other via their head domains, and they are capable of forming a structure of alternating XRCC4 and XLF molecules (Andres and Junop 2011; Hammel et al. 2011; Ropars et al. 2011; Wu et al. 2011). Ku, XRCC4/ligase IV, and XLF have a mismatched end (MEnd) ligase activity that ligates any pair of DNA ends, even ends with mismatched overhangs (Tsai et al. 2007). The proteins may form a megadalton protein-DNA complex containing Ku plus a filament of alternating molecules of XRCC4/ligase IV and XLF (Tsai and Chu 2013). The cooperative assembly of the filament may facilitate juxtaposition of the mismatched ends for ligation.

MEnd ligase activity is particularly robust for 3′ overhangs, which is relevant for V(D)J recombination, the pathway that generates immunological diversity (see the brief definition “V(D)J Recombination”). Recombination occurs by a pair of cleavages adjacent to two recombination signal sequences. The cleavages are catalyzed by the endonuclease RAG1/RAG2 (recombination-activating gene products 1 and 2) (McBlane et al. 1995). Each cleavage generates a blunt end adjacent to signal sequence and a hairpin end adjacent to protein-coding sequence. C-NHEJ then joins the blunt ends to each other in a precise reaction and the hairpin ends to each other in an error-prone reaction. In a complex with DNA-PKcs, the endonuclease Artemis opens the hairpin ends, either with a nick at the tip of the hairpin or an asymmetric nick that creates a palindromic 3′ single-stranded overhang (Ma et al. 2002). Terminal deoxynucleotidyl transferase may also add random

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<tr>
<th>Protein</th>
<th>Biochemical activity</th>
<th>Human disease</th>
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<td>Ku</td>
<td>DNA end binding</td>
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<tr>
<td>DNA-PKcs</td>
<td>DNA-dependent protein kinase, synopsis of DNA ends</td>
<td>Radiation sensitivity with severe combined immunodeficiency (van der Burg et al. 2009)</td>
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<td>XRCC4</td>
<td>DNA binding, partner of ligase IV</td>
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<td>Ligase IV</td>
<td>DNA ligase</td>
<td>Nijmegen breakage syndrome-like disorder (O’Driscoll et al. 2001)</td>
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<tr>
<td>XLF (Cernunnos)</td>
<td>DNA binding, promotion of mismatched end ligation</td>
<td>Radiation sensitivity with severe combined immunodeficiency (Ahnesorg et al. 2006; Buck et al. 2006)</td>
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<tr>
<td>PNKP</td>
<td>Poly(adenosine 5′-diphosphate)-ribose polymerase</td>
<td>Microcephaly and seizures (Shen et al. 2010)</td>
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<td>Artemis</td>
<td>Endonuclease, exonuclease</td>
<td>Radiation sensitivity with severe combined immunodeficiency (Moshous et al. 2001)</td>
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<td>Pol mu</td>
<td>DNA polymerase</td>
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<td>Pol lambda</td>
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nucleotides to the 3’ end. The MEnd ligase complex can ligate a mismatched 3’ overhang to preserve the nucleotide sequences from the palindromic 3’ overhang (P addition) or from the addition of random nucleotides (N addition). Mutations in C-NHEJ genes cause several human diseases (Table 3), including radiation sensitivity with severe combined immunodeficiency (RS-SCID), where SCID is due to the importance of DNA-PKcs, Artemis, and XLF in V(D)J recombination.

In addition to ends ending in hairpins, C-NHEJ must join DNA ends with disrupted termini that require enzymatic processing prior to ligation. Artemis has an intrinsic 5’–3’ exonuclease activity. Upon forming a complex with DNA-PKcs, Artemis acquires an endonuclease activity that cleaves 5’ and 3’ ssDNA overhangs (Ma et al. 2002). Polynucleotide kinase/phosphatase (PNKP) converts 5’-hydroxyl and 3’-phosphate DNA termini (such as those created by ionizing radiation) into ligatable 5’-phosphate and 3’-hydroxyl ends. PNKP requires XRCC4, thus linking its processing activity to ligation by ligase IV (Chappell et al. 2002; Koch et al. 2004; Mani et al. 2010). DNA polymerases μ and λ have been implicated in C-NHEJ by their interactions with Ku and XRCC4. Both enzymes are recruited to fill gaps when ends have partially complementary overhangs (Nick McElhinny et al. 2005).

C-NHEJ optimizes the preservation of DNA sequence by suppressing processing so that compatible DNA ends are joined precisely. For example, the blunt ends adjacent to V(D)J recombination signal sequences are joined without nucleotide addition or deletion virtually 100% of the time. In human cell extracts that recapitulate C-NHEJ in intact cells, blunt and cohesive ends are joined precisely, even though processing readily targets noncompatible ends to generate both nucleotide addition and deletion (Budman and Chu 2005). These observations suggest that C-NHEJ controls access of the processing enzymes to the DNA ends.

How does C-NHEJ prevent unnecessary processing of the ends? All polymerase and most nuclease activity require the presence of XRCC4/ligase IV (Budman et al. 2007). The processing enzymes polymerase μ, polymerase λ, and PNKP interact with XRCC4, which appears to grant access to the DNA ends. This mechanism ensures that XRCC4/ligase IV binds to the ends first and catalyzes ligation if processing is not required. The small fraction of nuclease activity in the absence of XRCC4/ligase IV could occur via recruitment and activation of Artemis by DNA-PKcs. Thus, C-NHEJ regulates processing via an ordered series of steps: binding by Ku and then DNA-PKcs, synopsis of the ends and DNA-PKcs autophosphorylation, release of the ends for binding by XRCC4/ligase IV and XLF, and finally XRCC4-dependent recruitment of PNKP and polymerase (Fig. 4).

Additional questions remain unanswered. Although Artemis participates in C-NHEJ, it is not known if other nucleases also contribute to processing of the ends. The MRN complex tethers DNA ends and contributes to end resection in A-NHEJ and HR. It is not known if MRN contributes to end processing during C-NHEJ. Perhaps, the complex of MRN and CtIP resects DNA ends before Ku binds to the ends, accounting for some of the deletions observed in C-NHEJ.

**Alternative End Joining (A-NHEJ)**

Evidence has accumulated for an alternative nonhomologous end-joining pathway (A-NHEJ) (Deriano and Roth 2013). Deletion of XRCC4 or ligase IV reveals robust alternative end joining during class switch recombination (Yan et al. 2007). Removal of portions of the RAG1 and RAG2 proteins reveals an alternative joining pathway during V(D)J recombination in NHEJ-deficient cells (Corneo et al. 2007). In the absence of XRCC4/ligase IV, chromosomal translocations occur with much greater frequency (Simsek and Jasin 2010).
A-NHEJ appears to be a distinct pathway, rather than a pathway cobbled together by substituting another repair protein for a missing C-NHEJ protein (Deriano and Roth 2013). The junctions created by A-NHEJ are not affected by whether Ku or XRCC4/ligase IV is absent. In the RAG mutants cited above, A-NHEJ is robust even in the presence of intact C-NHEJ. Finally, A-NHEJ may have evolved before C-NHEJ, since *E. coli* catalyze end joining by an A-NHEJ pathway but lack C-NHEJ proteins, such as Ku. Table 4 summarizes the proteins believed to be involved in A-NHEJ.

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**Fig. 4 Model for C-NHEJ.** Ku binds to the DNA ends and slides inward upon recruiting DNA-PKcs to the end. DNA-PKcs brings the ends together in a synaptic complex, which activates the DNA-PKcs kinase. DNA-PKcs undergoes autophosphorylation and releases the ends for binding by XRCC4/ligase IV (XL). (The red dot indicates where ligase IV interacts with XRCC4.) If the ends are ligatable with blunt or complementary overhangs, XL ligates the ends directly. If 3'-phosphate or 5'-hydroxyl groups have damaged the ends, XRCC4 recruits PNKP to repair the damage. XRCC4 and XLF assemble cooperatively into a protein-DNA filament to align the DNA ends, facilitating the ligation of DNA ends even if they have noncomplementary overhangs. DNA polymerases mu and lambda and nuclease activity process the ends.

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<td>See Table 1</td>
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<td>CtIP</td>
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<tr>
<td>PARP-1</td>
<td>Poly(ADP-ribose) polymerase</td>
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<td>XRCC1</td>
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The junctions created by A-NHEJ contain deletions, usually back to regions of microhomology. These deletions are significantly longer than those seen in C-NHEJ. Thus, A-NHEJ is the least conservative of the three repair pathways, serving as a backup system for HR and C-NHEJ.
Apparently, DSBs pose such a threat that cells evolved A-NHEJ despite its error-prone nature. On the other hand, it appears that A-NHEJ is primarily responsible for the chromosomal translocations seen in cancer.

Some elements of the A-NHEJ pathway are now known (Fig. 5). Recruitment of CtIP to the MRN complex activates Mre11 nuclease to resect the DNA ends (Lee-Theilen et al. 2011). Ligase III promotes A-NHEJ during chromosomal translocation (Simsek et al. 2011). XRCC1 forms a tight complex with ligase III (Caldecott et al. 1994), indicating that XRCC1 is also involved in A-NHEJ. Poly(ADP-ribose) polymerase 1 (PARP-1) facilitates A-NHEJ during class switch recombination (Robert et al. 2009). PARP-1, XRCC1, and DNA ligase III act together to join DNA ends. PARP-1 binds to ends, albeit with a lower affinity than Ku (Wang et al. 2006), consistent with a hierarchy that favors C-NHEJ over A-NHEJ.

Features of A-NHEJ remain unclear. What regulates the choice between A-NHEJ and the other pathways of HR and C-NHEJ? Upon binding to DNA, PARP-1 catalyzes transfer of 50–200 molecules of ADP-ribose from NAD+ to itself. Poly-ADP-ribosylation of PARP-1 results in its dissociation from the DNA end. Does PARP-1 self-modification recruit other A-NHEJ proteins?

**Conclusions**

To mitigate the danger posed by DNA DSBs, cells have evolved three pathways for DSB repair. HR is a conservative pathway that preserves DNA sequence, operating only in S and G2 phases of the cell cycle when an undamaged sister chromosome is available for recombination. C-NHEJ joins ends precisely if possible, but otherwise optimizes the preservation of DNA sequence. C-NHEJ plays key roles in V(D)J recombination and class switch recombination. A-NHEJ joins broken ends
not repaired by HR or C-NHEJ. Although this pathway may prevent death of the cell from an unreppaired chromosome, it generates chromosome translocations that lead to cancer.

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Cross-References

▶ Classical and Alternative End Joining
▶ DNA Repair
▶ DNA Repair Polymerases
▶ Eukaryotic RecA Homologs
▶ Hereditary Breast and Ovarian Cancer and Poly (ADP-Ribose) Polymerase Inhibition
▶ Homologous Recombination in Lesion Bypass
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▶ Regulation of DSB Repair by Cell-Cycle Signaling and the DNA Damage Response
▶ Single Strand Annealing
▶ Types of DNA Damage
▶ V(D)J Recombination

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