

The Mechanism of Human Nonhomologous DNA End Joining^{*[5]}

Published, JBC Papers in Press, November 12, 2007, DOI 10.1074/jbc.R700039200

Michael R. Lieber¹

From the Norris Comprehensive Cancer Center, Departments of Pathology, Biochemistry and Molecular Biology, Molecular Microbiology and Immunology, and Biological Sciences, University of Southern California Keck School of Medicine, Los Angeles, California 90089-9176

Double-strand breaks are common in all living cells, and there are two major pathways for their repair. In eukaryotes, homologous recombination is restricted to late S or G₂, whereas nonhomologous DNA end joining (NHEJ) can occur throughout the cell cycle and is the major pathway for the repair of double-strand breaks in multicellular eukaryotes. NHEJ is distinctive for the flexibility of the nuclease, polymerase, and ligase activities that are used. This flexibility permits NHEJ to function on the wide range of possible substrate configurations that can arise when double-strand breaks occur, particularly at sites of oxidative damage or ionizing radiation. NHEJ does not return the local DNA to its original sequence, thus accounting for the wide range of end results. Part of this heterogeneity arises from the diversity of the DNA ends, but much of it arises from the many alternative ways in which the nuclease, polymerases, and ligase can act during NHEJ. Physiologic double-strand break processes make use of the imprecision of NHEJ in generating antigen receptor diversity. Pathologically, the imprecision of NHEJ contributes to genome mutations that arise over time.

Overview of Nonhomologous DNA End Joining (NHEJ)²

All living cells have mechanisms for repairing double-strand DNA breaks (DSBs). Pathologic (disadvantageous) DSBs arise when the replication fork encounters a nick. Ionizing radiation particles create clusters of reactive oxygen species along their path, and these create DSBs. Reactive oxygen species themselves may cause DSBs. For dividing mammalian cells in culture, 5–10% appear to have at least one chromosome break (or chromatid gap) at any one time (1). Hence, the need to repair DSBs arises commonly (2).

There are two primary pathways for the repair of DSBs (Fig. 1). Homologous recombination occurs in during late S or G₂ of the cell cycle when the sister chromatid is close in proximity (3).

^{*} This minireview will be reprinted in the 2008 Minireview Compendium, which will be available in January, 2009.

^[5] The on-line version of this article (available at <http://www.jbc.org>) contains supplemental Figs. 1–6 and Refs. 1–3.

¹ To whom correspondence should be addressed: USC Keck School of Medicine, Rm. 5428, 1441 Eastlake Ave., MC9176, Los Angeles, CA 90089-9176. Tel.: 323-865-0568; Fax: 323-865-3019; E-mail: lieber@usc.edu.

² The abbreviations used are: NHEJ, nonhomologous DNA end joining; DSBs, double-strand DNA breaks; nt, nucleotide(s); DNA-PKcs, DNA-dependent protein kinase catalytic subunit; pol, polymerase(s); TdT, terminal deoxynucleotidyltransferase; MMEJ, microhomology-mediated end joining; RAG, recombination-activating gene.

NHEJ is the major pathway for the repair of DSBs because it can function throughout the cell cycle and because it does not require a homologous chromosome (3, 4). Rather, NHEJ involves rejoining of what remains of the two DNA ends, and the mechanism has evolved in a manner that tolerates nucleotide (nt) loss or addition at the rejoining site.

Because of the few nucleotides of resection and random addition necessary to get the two DNA ends into a ligatable configuration, NHEJ is distinctive among major DNA repair pathways for its imprecision. Hence, NHEJ leaves “information scars” at most sites of repair in vertebrates. The positive aspect of NHEJ is that the phosphodiester backbone and structural integrity of the chromosome are restored at sites that would otherwise result in loss of several hundreds of genes on entire chromosomal arms or segments. Attendant with the imprecision of NHEJ is the accumulation of randomly located mutations over time in the genome of each somatic cell of an organism.

Like most DNA repair processes, there are three enzymatic activities required for repair of DSBs by the NHEJ pathway: (a) nucleases to remove damaged DNA, (b) polymerases to aid in the repair, and (c) a ligase to restore the phosphodiester backbone (Fig. 2). In vertebrates, the Artemis-DNA-dependent protein kinase catalytic subunit (DNA-PKcs) complex becomes active as a 5′- and 3′-endonuclease when DNA-PKcs binds to a DSB DNA end. Polymerases μ and λ are two of the known polymerases for NHEJ. A complex of XLF (Cernunnos), XRCC4, and DNA ligase IV composes the ligase for NHEJ.

Key Components and the Order of Their Action in the Mechanism of NHEJ

When a DSB occurs during G₀, G₁, and early S phase, the Ku heterodimer (Ku70/Ku80) appears likely to be the first protein to bind. (During late S or G₂, there may be some competition between NHEJ and homologous recombination, although this is still an active area of investigation (5).) Ku must change conformation once it binds DNA because its interactions with other proteins such as DNA-PKcs are much stronger once the Ku-DNA end complex has formed (6). Ku is capable of interacting with the nuclease (Artemis-DNA-PKcs), the polymerases (μ and λ), and the ligase (XLF-XRCC4-DNA ligase IV). Hence, one can think of Ku as a tool belt protein that can stabilize any of a number of enzymatic activities at a DNA end (Fig. 2). One might assume that the nuclease, polymerases, and ligase function in this order (Fig. 3), and in some of the simpler scenarios, this probably occurs. However, each of these enzymes has a range of flexibility in their function that permits the NHEJ process to go to completion in any of a large number (hundreds) of ways, even when starting with two identical DNA ends. This flexibility accounts for the very diverse number of results, with some ends showing nt loss (1–10 nt, typically) and some joining sites (junctions) showing untemplated nt addition (0–3 nt, typically) (Fig. 2, lower). The next three sections describe in detail the flexibility of the nuclease, polymerase, and ligase components in NHEJ.

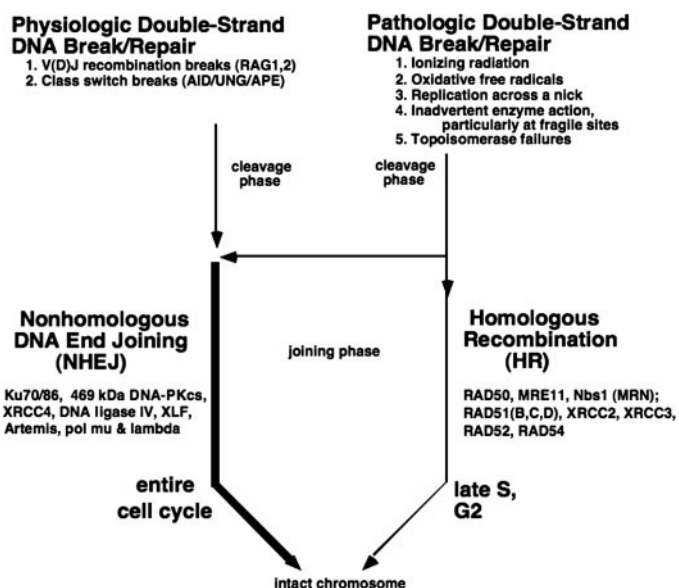


FIGURE 1. Nonhomologous DNA end joining pathway in the context of double-strand break repair. Five prominent causes of pathologic double-strand breaks in living cells are listed. Among multicellular eukaryotes, physiologic double-strand breaks are found only in the vertebrate immune system. V(D)J recombination is present in all true vertebrates and is initiated by an endonuclease complex composed of RAG1 and RAG2 (6). Class switch recombination is present in only a subset of these vertebrates and is initiated by a cytidine deaminase called activated-induced deaminase (AID). DSBs that arise in late S or G₂ of the cell cycle are often repaired at long regions (>100 bp) of homology using homologous recombination (although single-strand annealing also can occur) (3). However, the dominant pathway for the repair of double-strand breaks is called NHEJ, and this repair pathway can function at any time during the cell cycle. NHEJ does not use long stretches of homology, but the processing of the DNA ends can, in a minority of cases, be influenced by alignment of a few nt of homology called terminal microhomology (typically 1–4 nt in length). It should be noted that NHEJ proceeds even if there is no terminal microhomology. Important protein components of the repair pathways are listed. UNG, uracil-DNA glycosylase; APE, apurinic/apyrimidinic endonuclease.

The Artemis-DNA-PKcs Complex in the Nucleolytic Processing Steps of NHEJ

DNA-PKcs can bind to DNA ends with a K_D of 3×10^{-9} M, but this affinity improves to 3×10^{-11} M at a Ku-DNA end complex (7). Artemis and DNA-PKcs exist as a complex within cells (8), and this complex binds to Ku-DNA end complexes. When Ku moves internally, this permits DNA-PKcs to contact the DNA end, which then activates the serine/threonine kinase activity of DNA-PKcs (9–11). Activation of the kinase activity represents one of the simplest signal transduction systems because it permits DNA-PKcs to phosphorylate itself and Artemis (8, 12). The autophosphorylation of DNA-PKcs causes a conformational change in DNA-PKcs that regulates access by other NHEJ proteins (12–15). This conformational change in DNA-PKcs may alter the conformation of Artemis because now Artemis can function as a 5'- or 3'-endonuclease at overhangs (supplemental Fig. 1) (8, 16). This conformational change in Artemis also permits it to function as an endonuclease at a variety of other single/double-strand DNA structures, including DNA hairpins (8, 17), which turns out to be critical in the gene rearrangement process of the vertebrate immune system (called V(D)J recombination). One DNA-PKcs molecule can autophosphorylate itself in *cis* or another DNA-PKcs molecule in *trans*, and the relative ratio of *cis*- versus *trans*-phosphoryla-

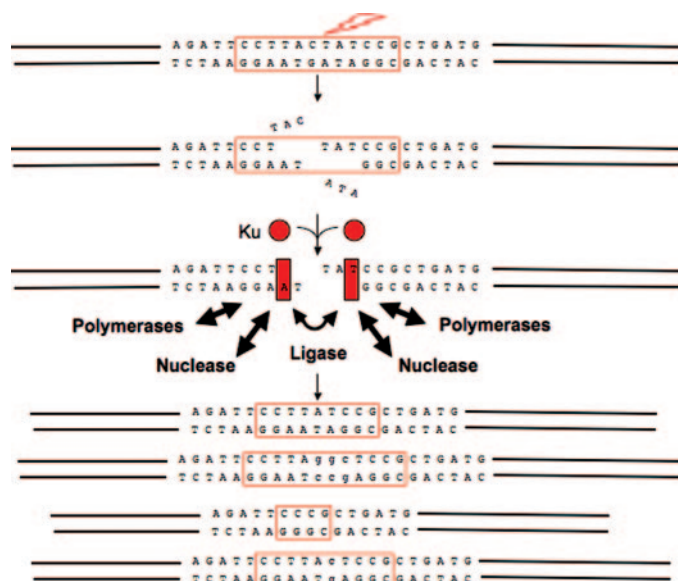


FIGURE 2. Loading of enzymatic activities at the two DNA ends in the nonhomologous DNA end joining pathway. Natural causes of pathologic double-strand breaks are expected to generate heterogeneous incompatible DNA ends with little or no terminal microhomology. Ku (red circles and red rectangles) is the most abundant DNA end-binding protein in eukaryotic cells and is a heterodimer of Ku70 and Ku80 (also called Ku86) (47). Ku has a toroidal shape (48) and can slide onto DNA ends that have diverse configurations (49). Ku likely changes conformation once it slides onto the DNA end (depicted by the red circle-to-rectangle shape change) because Ku complexes with DNA-PKcs are not detected except when Ku is bound to a DNA end (50). Once Ku is bound to the DNA end, it can improve the binding equilibrium of the nuclease, polymerases, and ligase of NHEJ. The nuclease, polymerases, and ligase appear capable of binding to a DNA end without Ku, but the binding is tighter with Ku present. The nuclease, polymerases, and ligase appear to be able to load in any order at either end. The only clearly identified nuclease thus far is the Artemis-DNA-PKcs complex. DNA-PKcs may serve additional functions of altering the DNA end configuration (15, 16) or phosphorylating other NHEJ components, although these are aspects for additional study. The polymerases for NHEJ include the pol X polymerases, pol μ and λ (51). The ligase of NHEJ consists of XLF, XRCC4, and DNA ligase IV (52, 53). The lower portion of the diagram shows four of many possible outcomes for the joining (the junction is highlighted in red boxes), and there are hundreds of other possible joining outcomes even for one pair of starting DNA ends. Polynucleotide kinase is known to interact with XRCC4, and this enzyme participates as necessary to convert 5'-OH groups to 5'-phosphate and to convert 3'-phosphate to 3'-OH groups (54).

tion is not known (supplemental Fig. 2) (18). A subset of DSBs created by ionizing radiation cannot be repaired without Artemis (19).

Polymerase (pol) X Polymerases in Template-independent and Template-dependent Synthesis Steps of NHEJ

Genetic and biochemical evidence for the role of pol X polymerases exists in yeast and mammalian cells (20, 21). In yeast, Pol4 is the only pol X polymerase. In mammalian cells, the pol X family consists of pol β , μ , and λ and terminal deoxynucleotidyltransferase (TdT). The latter three all contain BRCT domains, and all three function in NHEJ, whereas pol β does not. pol μ and λ share the most homology with *Saccharomyces cerevisiae* Pol4, and both appear to be expressed in mammalian somatic cells. TdT is expressed only in pre-B and pre-T cells.

pol λ , pol μ , and TdT share a range of structural similarities that correlate with their ratio of template-dependent versus template-independent synthesis (22). TdT carries out tem-

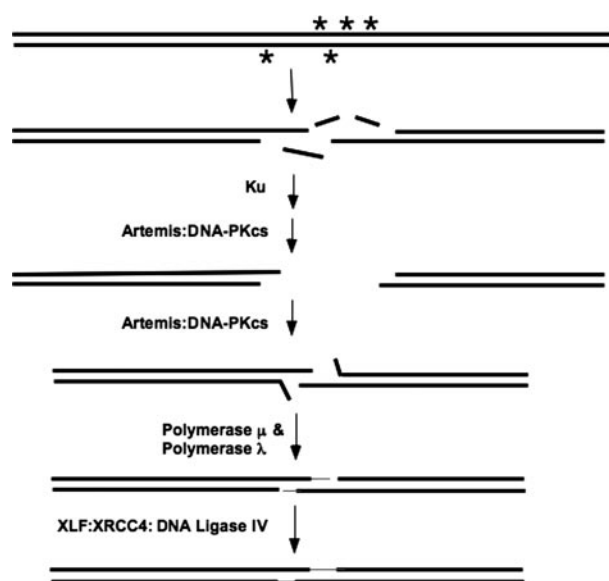


FIGURE 3. **Nonhomologous DNA end joining: a simple example.** The asterisks represent free radicals generated, for example, by the nearby passage of a particle of ionizing radiation. Some small fragments of DNA are lost. Ku binds to the remaining DSBs. In this example, Artemis:DNA-PKcs resects some of the overhangs. Fortuitous annealing occurs between the DNA ends, and Artemis:DNA-PKcs cleaves the flaps. Polymerase μ or λ can fill in the gaps (thin lines). The ligase complex ligates the nicks.

plate-independent synthesis, and pol λ is almost exclusively template-dependent. However, pol μ can carry out both template-dependent and template-independent synthesis in the presence of the physiologic divalent cation Mg^{2+} (23). pol μ and, to a greater extent, pol λ show some degree of template slippage, which can result in the generation of direct repeats, a feature seen at some sites of NHEJ (supplemental Fig. 3). The template-independent addition by pol μ could conceivably result in fold-back at the region of addition, followed by synthesis using the same strand as a template (supplemental Fig. 3, lower reaction). This could result in the generation of inverted repeats. The generation of direct and inverted repeats at a subset of NHEJ events *in vivo* is called T-nucleotide addition, where "T" stands for "templated" (24). The flexibility of pol μ and λ might account for T-nucleotides. TdT functions only during V(D)J recombination to add random nucleotides (called N-nucleotides) so as to increase the junctional diversity during the generation of the antigen receptor repertoire. The template-independent synthesis by pol μ is the likely basis for occasional antigen receptor junctional additions in lymphocytes from animals in which TdT has been knocked out (25, 26).

One might wonder why pol μ , a polymerase present in all somatic cells, would add nucleotides randomly. The evolutionary advantage of this becomes clear when considering a DSB in which there is no terminal microhomology between the two DNA ends. Random addition has the benefit of potentially generating 1 or 2 nt of terminal microhomology, permitting more efficient annealing of the ends and thereby facilitating NHEJ. Hence, use of terminal microhomology occurs in some fraction of NHEJ events when it exists between the two ends, and pol μ may manufacture such terminal microhomology when it does not exist at the two DNA ends. In addition, when 3'-overhangs are involved, pol μ may be more robust at this

type of fill-in from a region of minimal end-to-end annealing than any other polymerase (27, 28). Data for pol μ and the XRCC4:DNA ligase IV complex suggest that these two activities can bind a single Ku:DNA complex at one time (29, 30), raising the possibility of coordination of polymerase and ligase steps (29, 30).

XLf, XRCC4, and DNA Ligase IV in the Ligation Steps of NHEJ

DNA ligase IV can ligate double-stranded DNA molecules that have compatible overhangs or that are blunt (31). XRCC4 stabilizes the ligase IV protein in cells and improves its joining activity by increasing the efficiency of the adenylation of the ligase IV (31, 32). XLf stimulates the ability of XRCC4:DNA ligase IV to ligate in the presence of the physiologic divalent cation Mg^{2+} (33).

XRCC4:DNA ligase IV has a remarkable degree of flexibility, and there are several facets to this flexibility (supplemental Fig. 4). First, XRCC4:DNA ligase IV can ligate one strand independent of the other strand (34). For example, if the bottom strand is unligatable because of an uncleaved flap or a 5'-OH group, the top strand can still be ligated. Second, XRCC4:DNA ligase IV can ligate across gaps of even several nucleotides (23). Third, when Ku is present, XRCC4:DNA ligase IV can ligate some incompatible DNA ends that have short overhangs, albeit at lower efficiency than the ligation of ends that share 1 or more nt of terminal microhomology (23, 35). All of these aspects of the flexibility contribute to the range of DNA end configurations that XRCC4:DNA ligase IV can handle in its challenging role as the only ligase optimally suited for the repair of DSBs. Given that the two DNA ends of the DSB are likely to be in close proximity, each DNA end is likely to have a Ku molecule bound and associated with any of the three enzymatic activities, permitting nuclease, polymerase, and ligase action concurrently (supplemental Figs. 5 and 6).

Evolutionary Advantage of NHEJ Flexibility

At damage sites due to ionizing radiation, nt have been irreversibly lost at the instant of impact. Therefore, additional loss of a few more nt during the NHEJ repair process is of limited additional consequence; this is especially the case compared with the consequence of not restoring the chromosomal integrity. Tolerance of some level of imprecision has likely permitted the nuclease, polymerases, and ligase of NHEJ to evolve the substantial substrate and catalytic flexibility that they have.

Vertebrates have taken advantage of the imprecision and flexibility of NHEJ in the generation of antigen receptors for the adaptive portion of the immune system. In V(D)J recombination, the imprecision at the V-to-D and D-to-J joining sites (junctions) markedly increases the amount of potential diversity that would otherwise be limited simply to the various combinations of V, D, and J segments.

Recent work has shown that many prokaryotes have an NHEJ system that may be somewhat simpler than the one in eukaryotes, but which serves the same function (36–38). Hence, nearly all living cells have an NHEJ system, illustrating the importance of this general aspect of DNA repair.

Is NHEJ a Collection of Subpathways and Are There Alternative End Joining Pathways?

Some DNA end configurations might require only the ligase complex, XLF·XRCC4·DNA ligase IV. Other end configurations might require the polymerase complex followed by the ligase complex. Therefore, one may best think of NHEJ as initiating at a Ku·DNA end complex. Then Ku, functioning in a tool belt manner, recruits whatever enzymatic activities (typically nuclease, polymerase, kinase/phosphatase, or ligase activities) that are needed to arrive at a repair of the DSB (6). This alternative order and use of enzymes within NHEJ are best regarded as flexibility rather than distinct subpathways. The ligase, nuclease, and polymerase can each function without Ku in biochemical studies (8, 23, 34), and some *in vivo* data might be consistent with this (39, 40). Hence, some end configurations might join with only the XLF·XRCC4·ligase IV complex and without Ku, but at substantially reduced efficiency.

This latter way of viewing the flexibility of NHEJ may explain some *in vivo* data suggesting a DNA-PKcs-independent pathway or other independencies. In mice lacking one of the NHEJ components, especially DNA ligase IV, the presumption has been that the entire NHEJ pathway is blocked (41). However, the other NHEJ components are still present, and under circumstances in which NHEJ cannot go to completion, enzymes from other pathways might be expected to participate, to the extent that their enzymatic properties permit. For example, in a ligase IV-null cell, if the polymerase activities are able to synthesize for sufficient lengths to separate the top strand nick from the bottom strand nick (with duplex DNA between the nicks), then ligase I or III would be adequate to complete the joining. Outside of the context of an NHEJ mutant cell, this “backup” use of another ligase might be very rare. The rate of these alternatives or backup routes to joining relative to wild-type NHEJ is not clear; however, these alternatives do not appear capable of functioning at the level of NHEJ in response to ionizing radiation or V(D)J recombination carried out by wild-type RAG proteins (42). In class switch recombination, the involved sequences are rich in specific repeats that may permit the overhangs at the two DNA ends to be aligned, extended with polymerase, and ligated by ligase I or III in place of ligase IV (43). The fact that these repeats are not usually used for joining suggests that NHEJ is responsible for the large majority of end joining in class switch recombination.

The most commonly discussed alternative end joining pathway to NHEJ is called microhomology-mediated end joining (MMEJ), which is a somewhat confusing name, given that a subset of NHEJ events also uses 1–4 nt of terminal microhomology (44). MMEJ requires terminal microhomology (whereas microhomology is optional in NHEJ), and the lengths of the microhomology (often >5 nt) are somewhat longer than those used in NHEJ. The ligase for a subset of MMEJ events is ligase I, but that for others is ligase IV in yeast (44). In mammalian cells, there is evidence for ligase III involvement (45), illustrating that MMEJ, and perhaps other alternative routes to joining, may represent merely the possibilities that can arise when the full set of NHEJ components is not present, but that are not normally of substantial physiologic relevance. This seems likely

given that the types of pathologic DSBs that arise naturally, such as with ionizing radiation and oxidative damage, would almost never generate the pairs of DNA ends that are required for MMEJ or many other alternative routes, *viz.* ends that share several nt of terminal microhomology. The ligase III-dependent joining was shown recently to decrease markedly in nondividing cells (46), which is exactly the opposite of what evolution would select for in an end joining pathway. Therefore, in cells mutated for NHEJ, other enzymes may participate, but with a requirement of uncommon extents of and reliance upon microhomology. Rather than calling such events MMEJ, it would be less confusing to call these events ligase IV-independent NHEJ or Ku-independent NHEJ, etc.

Concluding Comments and Future Issues

NHEJ arose early in evolution and is present in many prokaryotes and all eukaryotes. NHEJ is imprecise at the local sequence level, but efficient at restoring chromosomal structural integrity. The enzymatic aspects of NHEJ are becoming clearer, but still include mechanistic uncertainties. At a site of a DSB, it is not yet clear what chromatin modifications are required to permit NHEJ and how these chromatin changes are achieved. Coordination between the completion of the DSB repair and the cell cycle is another area for continuing study. During DNA replication, it is not yet clear what determines whether a given DSB is repaired by NHEJ versus homologous recombination. Therefore, there is still much to be learned about this relatively recently described DNA repair pathway.

Acknowledgments—I thank Drs. K. Schwarz, D. Shibata, and X. Cui for comments on the manuscript.

REFERENCES

- Lieber, M. R., and Karanjawala, Z. E. (2004) *Nat. Rev. Mol. Cell Biol.* **5**, 69–75
- Li, H., Vogel, H., Holcomb, V. B., Gu, Y., and Hasty, P. (2007) *Mol. Cell Biol.* **27**, 8205–8214
- Sonoda, E., Hocegger, H., Saberi, A., Taniguchi, Y., and Takeda, S. (2006) *DNA Repair* **5**, 1021–1029
- Moore, J. K., and Haber, J. E. (1996) *Mol. Cell Biol.* **16**, 2164–2173
- Adachi, N., Ishino, T., Ishii, Y., Takeda, S., and Koyama, H. (2001) *Proc. Natl. Acad. Sci. U. S. A.* **98**, 12109–12113
- Lieber, M. R., Yu, K., and Raghavan, S. C. (2006) *DNA Repair* **5**, 1234–1245
- West, R. B., Yaneva, M., and Lieber, M. R. (1998) *Mol. Cell Biol.* **18**, 5908–5920
- Ma, Y., Pannicke, U., Schwarz, K., and Lieber, M. R. (2002) *Cell* **108**, 781–794
- Hammarsten, O., DeFazio, L. G., and Chu, G. (2000) *J. Biol. Chem.* **275**, 1541–1550
- Chu, G. (1997) *J. Biol. Chem.* **272**, 24097–24100
- Yoo, S., and Dynan, W. S. (1999) *Nucleic Acids Res.* **27**, 4679–4686
- Meek, K., Gupta, S., Ramsden, D. A., and Lees-Miller, S. P. (2004) *Immunol. Rev.* **200**, 132–141
- Uematsu, N., Weterings, E., Yano, K., Morotomi-Yano, K., Jakob, B., Taucher-Scholz, G., Mari, P. O., van Gent, D. C., Chen, B. P., and Chen, D. J. (2007) *J. Cell Biol.* **177**, 219–229
- Jovanovic, M., and Dynan, W. S. (2006) *Nucleic Acids Res.* **34**, 1112–1120
- Goodarzi, A. A., Yu, Y., Riballo, E., Douglas, P., Walker, S. A., Ye, R., Harer, C., Marchetti, C., Morrice, N., Jeggo, P. A., and Lees-Miller, S. P. (2006) *EMBO J.* **25**, 3880–3889

16. Niewolik, D., Pannicke, U., Lu, H., Ma, Y., Wang, L. C., Kulesza, P., Zandi, E., Lieber, M. R., and Schwarz, K. (2006) *J. Biol. Chem.* **281**, 33900–33909
17. Ma, Y., Schwarz, K., and Lieber, M. R. (2005) *DNA Repair* **4**, 845–851
18. Meek, K., Douglas, P., Cui, X., Ding, Q., and Lees-Miller, S. P. (2007) *Mol. Cell. Biol.* **27**, 3881–3890
19. Riballo, E., Kuhne, M., Rief, N., Doherty, A., Smith, G. C., Recio, M. J., Reis, C., Dahm, K., Fricke, A., Krempler, A., Parker, A. R., Jackson, S. P., Genery, A., Jeggo, P. A., and Lobrich, M. (2004) *Mol. Cell* **16**, 715–724
20. Wilson, T. E., and Lieber, M. R. (1999) *J. Biol. Chem.* **274**, 23599–23609
21. Bertocchi, B., DeSmet, A., Weill, J.-C., and Reynaud, C. A. (2006) *Immunity* **25**, 31–41
22. Moon, A. F., Garcia-Diaz, M., Batra, V. K., Beard, W. A., Bebenek, K., Kunkel, T. A., Wilson, S. H., and Pedersen, L. C. (2007) *DNA Repair* **6**, 1709–1725
23. Gu, J., Lu, H., Tippin, B., Shimazaki, N., Goodman, M. F., and Lieber, M. R. (2007) *EMBO J.* **26**, 1010–1023
24. Jaeger, U., Bocskor, S., Le, T., Mitterbauer, G., Bolz, I., Chott, A., Kneba, A., Mannhalter, C., and Nadel, B. (2000) *Blood* **95**, 3520–3529
25. Gilfillan, S., Dierich, A., Lemeur, M., Benoist, C., and Mathis, D. (1993) *Science* **261**, 1755–1759
26. Komori, T., Okada, A., Stewart, V., and Alt, F. (1993) *Science* **261**, 1171–1175
27. Daley, J. M., Vander Laan, R. L., Suresh, A., and Wilson, T. E. (2005) *J. Biol. Chem.* **280**, 29030–29037
28. Daley, J. M., Palmbo, P. L., Wu, D., and Wilson, T. E. (2005) *Annu. Rev. Genet.* **39**, 431–451
29. Tseng, H. M., and Tomkinson, A. E. (2002) *J. Biol. Chem.* **277**, 45630–45637
30. Mahajan, K. N., Nick McElhinny, S. A., Mitchell, B. S., and Ramsden, D. A. (2002) *Mol. Cell. Biol.* **22**, 5194–5202
31. Grawunder, U., Wilm, M., Wu, X., Kulesza, P., Wilson, T. E., Mann, M., and Lieber, M. R. (1997) *Nature* **388**, 492–495
32. Modesti, M., Hesse, J. E., and Gellert, M. (1999) *EMBO J.* **18**, 2008–2018
33. Gu, J., Lu, H., Tsai, A. G., Schwarz, K., and Lieber, M. R. (2007) *Nucleic Acids Res.* **35**, 5755–5762
34. Ma, Y., Lu, H., Tippin, B., Goodman, M. F., Shimazaki, N., Koiwai, O., Hsieh, C.-L., Schwarz, K., and Lieber, M. R. (2004) *Mol. Cell* **16**, 701–713
35. Tsai, C. J., Kim, S. A., and Chu, G. (2007) *Proc. Natl. Acad. Sci. U. S. A.* **104**, 7851–7856
36. Stephanou, N. C., Gao, F., Bongiorno, P., Ehrst, S., Schnappinger, D., Shuman, S., and Glickman, M. S. (2007) *J. Bacteriol.* **189**, 5237–5246
37. Pitcher, R. S., Brissett, N. C., and Doherty, A. J. (2007) *Annu. Rev. Microbiol.* **61**, 259–282
38. Gong, C., Bongiorno, P., Martins, A., Stephanou, N., Zhu, H., Shuman, S., and Glickman, M. S. (2005) *Nat. Struct. Mol. Biol.* **12**, 304–312
39. Weinstock, D. M., Brunet, E., and Jasin, M. (2007) *Nat. Cell Biol.* **9**, 978–981
40. van Heemst, D., Brugmans, L., Verkaik, N., and van Gent, D. C. (2004) *DNA Repair* **3**, 43–50
41. Ferguson, D. O., and Alt, F. W. (2001) *Oncogene* **20**, 5572–5579
42. Corneo, B., Deriano, L., Cui, X., Klein, L., Wendland, R., Wong, S., Arnal, S., Weller, G., Pancake, B., Brandt, V., Meek, K., and Roth, D. B. (2007) *Nature* **449**, 483–486
43. Yan, C. T., Boboila, C., Souza, E. K., Franco, S., Hickernell, T. R., Murphy, M., Gumaste, S., Geyer, M., Zarrin, A. A., Manis, J. P., Rajewsky, K., and Alt, F. W. (2007) *Nature* **449**, 478–482
44. Ma, J. L., Kim, E. M., Haber, J. E., and Lee, S. E. (2003) *Mol. Cell. Biol.* **23**, 8820–8828
45. Wang, H., Rosidi, B., Perrault, R., Wang, M., Zhang, L., Windhofer, F., and Iliakis, G. (2005) *Cancer Res.* **65**, 4020–4030
46. Windhofer, F., Wu, W., Wang, M., Singh, S. K., Saha, J., Rosidi, B., and Iliakis, G. (2007) *Int. J. Radiat. Oncol. Biol. Phys.* **68**, 1462–1470
47. Downs, J. A., and Jackson, S. P. (2004) *Nat. Rev. Mol. Cell Biol.* **5**, 367–378
48. Walker, J. R., Corpina, R. A., and Goldberg, J. (2001) *Nature* **412**, 607–614
49. Falzon, M., Fewell, J., and Kuff, E. L. (1993) *J. Biol. Chem.* **268**, 10546–10552
50. Yaneva, M., Kowalewski, T., and Lieber, M. R. (1997) *EMBO J.* **16**, 5098–5112
51. Povirk, L. F. (2006) *DNA Repair* **5**, 1199–1212
52. Buck, D., Malivert, L., de Chasseval, R., Barraud, A., Fondanèche, M.-C., Sanal, O., Plebani, A., Stéphan, J.-L., Hufnagel, M., le Deist, F., Fischer, A., Durrandy, A., de Villartay, J.-P., and Revy, P. (2006) *Cell* **124**, 287–299
53. Ahnesorg, P., Smith, P., and Jackson, S. P. (2006) *Cell* **124**, 301–313
54. Chappell, C., Hanakahi, L. A., Karimi-Busheri, F., Weinfeld, M., and West, S. C. (2003) *EMBO J.* **21**, 2827–2832

The Mechanism of Human Nonhomologous DNA End Joining
Michael R. Lieber

J. Biol. Chem. 2008, 283:1-5.

doi: 10.1074/jbc.R700039200 originally published online November 12, 2007

Access the most updated version of this article at doi: [10.1074/jbc.R700039200](https://doi.org/10.1074/jbc.R700039200)

Alerts:

- [When this article is cited](#)
- [When a correction for this article is posted](#)

[Click here](#) to choose from all of JBC's e-mail alerts

Supplemental material:

<http://www.jbc.org/content/suppl/2007/11/14/R700039200.DC1>

This article cites 54 references, 23 of which can be accessed free at
<http://www.jbc.org/content/283/1/1.full.html#ref-list-1>