Minireview

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 279, No. 17, Issue of April 23, pp. 16895–16898, 2004
Printed in U.S.A.

DNA Replication Fidelity*

Published, JBC Papers in Press, February 26, 2004,
DOI 10.1074/jbc.R400006200

Thomas A. Kunkel‡

From the Laboratory of Molecular Genetics and Laboratory of Structural Biology, NIEHS, National Institutes of Health, Research Triangle Park, North Carolina 27709

When describing the structure of the DNA double helix, Watson and Crick (1) wrote, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." Fifty years later, interest in the fidelity of DNA copying mechanisms remains high because the balance between correct and incorrect DNA synthesis is relevant to a great deal of biology. High fidelity DNA synthesis is beneficial for maintaining genetic information over many generations and for avoiding mutations that can initiate and promote human diseases such as cancer and neurodegenerative diseases. Low fidelity DNA synthesis is beneficial for the evolution of species, for generating diversity leading to increased survival of viruses and microbes when subjected to changing environments, and for the development of a normal immune system. What was not yet appreciated 50 years ago was the large number and amazing diversity of transactions involving DNA synthesis required to faithfully replicate genomes and to stably maintain them in the face of constant challenges from cellular metabolism and the external environment. To perform these tasks, cells harbor multiple DNA polymerases (2, 3), many of which have only been discovered in the past 5 years and whose cellular functions are not fully understood. These polymerases differ in many features including their fidelity. This diversity and the sequence complexity of genomes provide the potential to vary DNA synthesis error rates over a wider range than was appreciated a few years ago. This article reviews major concepts and recent progress on DNA replication fidelity with additional perspectives found in longer reviews cited throughout.

How Accurate Is DNA Synthesis?

Studies of bacteriophage and Escherichia coli replication in the absence of DNA mismatch repair and external environmental stress suggest that the base substitution error rate of the replication machinery *in vivo* is in the range of 10^{-7} to 10^{-8} (4). Eukaryotic DNA replication is likely to be at least this accurate (5). High chromosomal replication fidelity *in vivo* is matched *in vitro* by the accuracy of *E. coli* and human replication complexes and replicative polymerases that have intrinsic proofreading exonuclease activities (Fig. 1, *top left*). Error rates during DNA synthesis are in the 10^{-6} to 10^{-8} range for replicative polymerases in family A (*e.g.* T7 Pol), family B (*e.g.* T4 Pol, Pol δ, Pol ϵ) and family C (*e.g. E. coli* Pol III). Comparisons with error rates for their proofreading-defective derivatives (Fig. 1, designated A^-, B^-, C^-, and RT^-, for viral reverse transcriptase) reveal that high fidelity typically results from 10^4 to 10^6-fold polymerase selectivity for inserting correct rather than incorrect nucleotides, followed by excision of 90–99.9% of base-base mismatches by exonucleases that are either intrinsic to the polymerase (*e.g.* T7 Pol, T4 Pol, Pol δ, Pol ϵ) or encoded by a separate gene (*e.g.* the ϵ subunit of *E. coli* Pol III).

Genome stability also requires the ability to repair DNA damage that comes in many forms and is repaired by several different pathways (6), most of which require DNA synthesis to fill gaps created when lesions are excised. Error rates for repair reactions have not yet been extensively studied. Gap filling during mismatch repair, nucleotide excision repair, and long patch base excision repair (BER)[1] is performed by A and B family polymerases with intrinsic proofreading activity. Thus, these repair reactions are predicted to be accurate, consistent with known roles in suppressing damage-induced mutagenesis. Repair requiring filling gaps of one or a few nucleotides, such as "short patch" BER and repair of DNA double strand breaks by non-homologous end joining, use family X polymerases. On average, these are less accurate than replicative polymerases (Fig. 1) partly, but not exclusively, due to a lack of intrinsic proofreading.

Lesions that escape repair can potentially reduce replication fidelity. Translesion synthesis (TLS) polymerases copy past lesions in DNA that block the major replicative polymerases (7–11). One is the B family member Pol ζ, and others are in the Y family, members of which are found in organisms from bacteria to man (*e.g. E. coli* Pol IV and V and mammalian Pol η, Pol ι, and Pol κ). Also lacking proofreading activity, these are the least accurate DNA polymerases, with misinsertion and base substitution error rates when copying undamaged templates that generally range from 10^{-1} to 10^{-3} (Fig. 1, *top*). The most striking violation of Watson-Crick base pairing rules is exhibited by Pol ι, which inserts dGTP opposite template T even more efficiently than it inserts A opposite T (12–14), *i.e.* its error rate for this mispair approaches 1 (Fig. 1). That base substitution error rates of wild-type DNA polymerases vary over a million-fold range is perhaps the biggest change in our view of DNA synthesis fidelity in the past decade.

Correct DNA Synthesis

Crystal structures (Refs. 15–22 and references therein) reveal that polymerase binding to DNA strongly reshapes the primer-template, *e.g.* the backbone at the templating base can be bent by 90°. In the absence of a dNTP, polymerases are often, but not invariably (20–22), in an "open" conformation with the active site not yet assembled. Binding of a correct dNTP induces large changes in the relative positions of polymerase subdomains and more subtle changes in amino acid side chains and in DNA conformation. These dNTP-induced changes result is a "closed" ternary complex containing a binding pocket that snugly surrounds the nascent base pair and an active site containing the αP of the incoming dNTP poised for the in-line nucleophilic attack of the 3′-OH of the primer. Ternary complexes of several different polymerases have an arrangement of reactive groups consistent with a two-metal ion mechanism for nucleotidyl transfer that may be common to all polymerases (23). Within this framework, the following ideas have been considered most relevant to fidelity.

Base-Base Hydrogen Bonding

Ever since Watson and Crick (1) noted that correct base pairs form specific hydrogen bonds, these have been thought to contribute to the specificity of DNA synthesis. That base-base hydrogen bonding does contribute to fidelity is clear, but the contribution appears to be relatively small and may be polymerase-dependent (24). By the late 1970s (25), the idea had emerged that if DNA polymerases merely acted as "zippers" to polymerize those dNTPs whose presence in the active site was determined by base-base hydrogen bonding, selectivity should depend on differences in free energy between complementary and non-complementary base pairs. In aqueous solution, these differences are 0.2–4 kcal/mol, which can account for one incorrect insertion for about 10 to a few hundred correct insertions. Error rates are in this range for Y family members (Fig. 1, *top*), suggesting that TLS enzymes may have relaxed geometric selectivity (see below) and primarily depend on base-base hydrogen bonding as the major determinant of

* This minireview will be reprinted in the 2004 Minireview Compendium, which will be available in January, 2005.

‡ To whom correspondence should be addressed. Tel.: 919-541-2644; Fax: 919-541-7613; E-mail: kunkel@niehs.nih.gov.

[1] The abbreviations used are: BER, base excision repair; TLS, translesion synthesis.

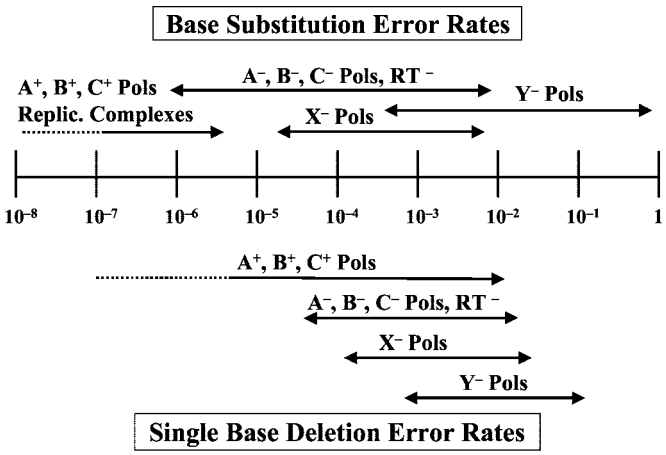

FIG. 1. **Replication error rates.** Shown are the ranges of error rates for single base substitutions (*top*) or deletions (*bottom*) as determined for replication by the *E. coli* or human replication machinery (SV40 system) and for gap filling DNA synthesis by polymerases. Kinetic studies of dNTP misinsertion rates typically yield values similar to the base substitution error rates shown. The wide range of error rates for each category reflects (at least) three variables: the polymerase, the composition of the error (*e.g.* 12 base substitutions are possible), and the local sequence context. Strand slippage accounts for certain unusually high insertion/deletion error rates, and transient misalignment (56, 57) accounts for high base substitution rates at the 5′ ends of mononucleotide runs (see text). The *dashed lines* are intended to imply that error rates could be as low or even lower than indicated, but rates in these ranges are difficult to quantify with the biochemical approaches currently used.

fidelity. These ideas are supported by structural information (20, 21, 26–28) and by a report (29) that the insertion fidelity of yeast Pol η is severely impaired with difluorotoluene, a nonpolar isosteric analog of thymine that is unable to form Watson-Crick hydrogen bonds with adenine.

Water Exclusion and Enthalpy-Entropy Compensation

Most polymerases have higher fidelity than can be explained by free energy differences between correct and incorrect base pairs in aqueous solution. One explanation (30) is that these enzymes amplify free energy differences between correct and incorrect base pairs by partially excluding water from the active site, thus increasing enthalpy differences and reducing entropy differences and improving fidelity. This hypothesis is consistent with the observation that in the crystal structure of the Y family, low fidelity *Sso* Dpo4 (27, 28), the active site (Fig. 2, *B* and *C*) is more accessible to solvent than are the active sites of more accurate polymerases in other families (*e.g.* Pol β) (Fig. 2*A*).

Geometric Selection for Correct Shape and Size

Polymerases in families A, B, X, and RT have nascent base pair binding pockets that tightly accommodate a correct Watson-Crick base pair (Fig. 2*A* and additional images in Refs. 15–19 and references therein). This tight fit is consistent with a concept that emerged about 25 years ago (reviewed in Refs. 15 and 31) that nucleotide selectivity largely depends on geometric selection for the shape and size of correct Watson-Crick base pairs. The geometries of A·T and G·C base pairs are remarkably similar to each other but differ from mismatched base pairs (15, 19, 24, 31, 32). Abnormal geometry is thought to result in steric clashes in and around the active site that preclude efficient catalysis. This hypothesis is supported by numerous studies with base analogs (24, 32). As one example, nonpolar bases that mimic the size and shape of normal bases but are unable to form Watson-Crick hydrogen bonds are incorporated by some polymerases with selectivity almost as high as for normal bases, suggesting that base pair shape and size may contribute more to the fidelity of some accurate DNA polymerases than does base-base hydrogen bonding. Small pyrimidine-pyrimidine mispairs that might otherwise fit into the binding pocket may be enlarged by water molecules that hydrogen bond to their Watson-Crick pairing edges. This effect of solvation is suggested to provide a strong force for steric exclusion (32). The importance of geometry to fidelity is also implied by the altered fidelity of polymerases with non-conservative replacements of amino acids that

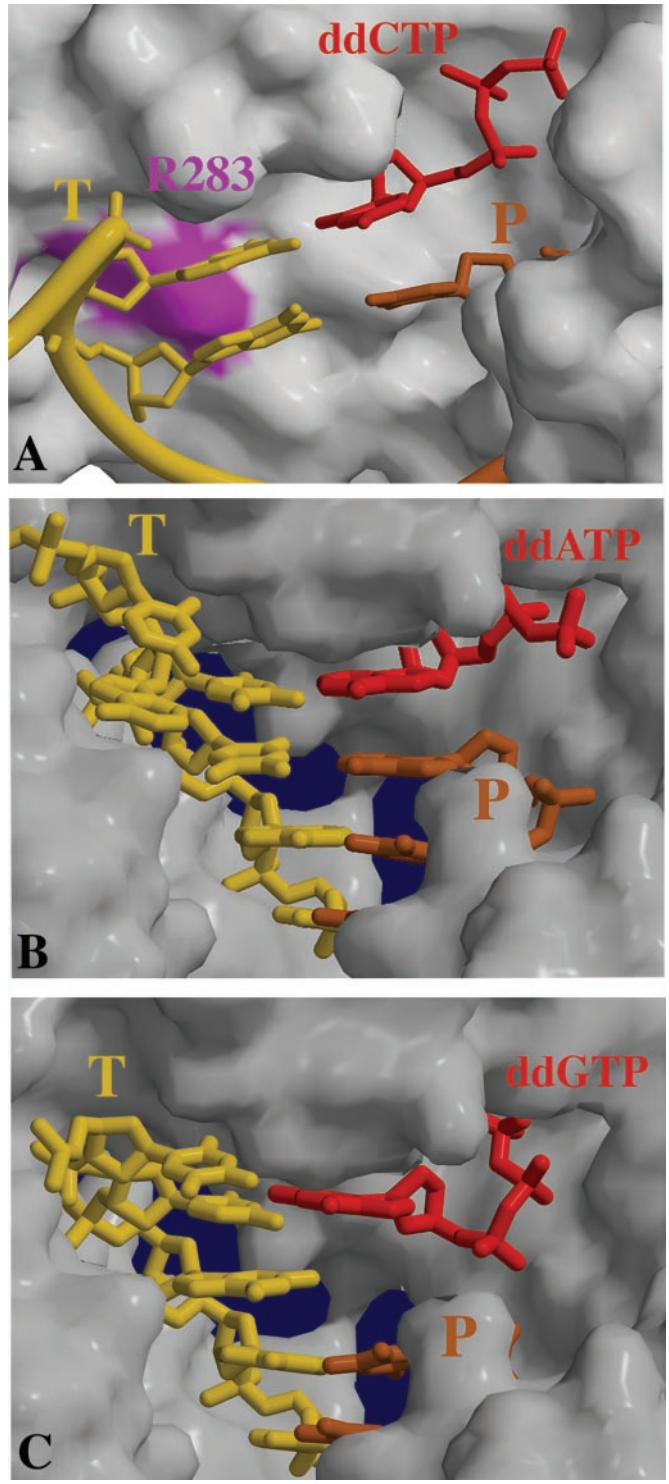

FIG. 2. **Structures of Pol β and *Sulfolobus solfataricus* Dpo4.** *A*, Pol β nascent base pair binding pocket with the molecular surface of Arg283 in *magenta*. *B*, correct base pair in the Dpo4 active site. *C*, a misaligned base pair in Dpo4 active site. In all three *panels t*he proteins (*gray*) are in surface representation, the template (*T*) and primer (*P*) strands are *yellow* and *light brown*, respectively, and the incoming triphosphate is *red*. Reproduced from Ref. 8 with permission from Elsevier.

are in and adjacent to the polymerase active site (*e.g.* see Refs. 15 and 24). Polymerase interactions important to fidelity occur with the minor groove edges of the templating nucleotide and the primer-terminal base pair (*e.g. magenta* patch in Fig. 2*A*), with the base, sugar, and triphosphate moieties of the incoming nucleotide, and with the template strand nucleotide immediately 5′ to the templating nucleotide. Altered fidelity also results from changing amino acids that interact several base pairs upstream in the duplex tem-

plate-primer as well as amino acids that do not directly contact the DNA or dNTP. The latter changes may indirectly alter geometry or perturb steps in the reaction cycle not captured in crystal structures. The importance of size and shape is also implied by the generally low fidelity of Y family polymerases and their abilities to copy DNA templates containing lesions that distort helix geometry. In fact, the crystal structure of a ternary complex of *Sso* Dpo4 (27) reveals little contact with DNA and an active site (Fig. 2*B*) comprised of small side chains and flexible enough to accommodate two bases at the same time (Fig. 2*C*). This flexibility may be critical for bypassing lesions that distort geometry.

dNTP Binding Affinity, dNTP-induced Conformational Changes, Chemistry

Kinetic studies (reviewed in Refs. 15, 19, 33–36) have established that fidelity depends on differences in the binding affinities and insertion rates of incorrect *versus* correct dNTPs. The molecular events that limit incorrect and correct nucleotide insertion remain an active area of investigation and may depend on the polymerase, the base pair, and the DNA sequence context. It is generally believed that nucleotide insertion is governed by an unidentified dNTP-induced conformational change and/or chemistry. A recent study (36) reveals that the catalytic efficiency for correct dNTP insertion by different polymerases varies by 10^7-fold, with the least accurate polymerases having the lowest efficiencies. In contrast, catalytic efficiencies for incorrect insertions by these polymerases vary over a much narrower range. The divergent catalytic efficiencies for correct insertion are due to the different insertion rates exhibited by DNA polymerases because they generally bind the correct dNTP with similar affinities (19, 36). A comparison of crystallographic structures indicates that the electrostatic environment of the phosphates of the incoming correct dNTP differs among polymerases with different fidelities (19). These results suggest that fidelity is primarily governed by the ability to insert the correct nucleotide (36) and focus attention on the conformational changes and interactions needed to achieve and stabilize the transition state. The above mentioned dNTP-induced "open to closed" conformational change inferred from crystallography was originally considered as a possible rate-limiting step, but recent studies (37–39) suggest that this may not be the case for DNA polymerase β. Also, Pol λ has similar base substitution fidelity to Pol β, yet unlike Pol β it is in a closed conformation even without a bound dNTP (22). Moreover, certain Y family polymerases are suggested to be in a closed conformation without dNTP (Refs. 20 and 21 but also see comments in Ref. 28), yet kinetic data (40) have emphasized the importance of a dNTP-induced conformational change preceding chemistry to the fidelity of Pol η. These observations suggest that fidelity may be modulated by subtle conformational changes that result in optimal positioning of active site residues and that these may differ for correct and incorrect nucleotides. Indeed, a recent study (41) using stopped-flow fluorescence has suggested that the conformations adopted during correct and incorrect nucleotide incorporation are distinct and that specificity for the correct substrate could be generated if these conformational differences persist into the transition states, consistent with an induced fit mechanism (for further discussions, see Refs. 41 and 42).

Rare Base Substitution Errors and Dealing with Damage

When copying undamaged DNA, polymerases generate base substitution errors at readily detectable rates, demonstrating that mispairs can bind with the stability and geometry ultimately needed for catalysis. These may be minor forms resulting from wobble base pairing (*e.g.* Ref. 43), tautomerization, ionization, or *anti-syn* rotations of bases (33). The most well known example of the latter is synthesis involving 8-oxy-G, a common by-product of oxidative metabolism. With many polymerases, 8-oxy-dG in a *syn* conformation forms a Hoogsteen pair with adenine, ultimately generating transversion mutations (reviewed in Refs. 44 and 45). However, Pol β avoids this inaccurate reaction by flipping the 5′-phosphate backbone of the templating nucleotide 180°, relieving a steric clash with the oxygen at C-8 and allowing non-mutagenic pairing of incoming dCTP with 8-oxy-dG in the Watson-Crick *anti* conformation (46). Yet a different, non-mutagenic example of Hoogsteen base pairing is seen for *Sso* Dpo4 bypass of a *cis-syn* thymine-thymine dimer. In a ternary crystal structure complex (28), the 3′ T of the dimer forms a Watson-Crick base pair with ddATP in the *anti* conformation at the active site whereas the 5′ T forms a Hoogsteen base pair with ddATP in its *syn* conformation. Thus Hoogsteen base pairing is one possible solution to correct templating by the 5′ T despite its covalent linkage to the preceding base. This may have implications for the fidelity of lesion bypass, because both Dpo4 and human Pol η have higher fidelity at the 5′ T of a dimer than at the 3′ T, and surprisingly, the fidelity of human Pol η is slightly higher at the 5′ T of a dimer than at the equivalent undamaged T (47). These two examples illustrate different solutions for performing DNA synthesis with damaged substrates that have mutagenic potential. Numerous studies have examined the nucleotide insertion specificity of lesion bypass polymerases opposite other lesions (Refs. 8, 10–14, 48, 49 and references therein). However, the multiplicity of polymerases and the large number of structurally distinct lesions generated by cellular metabolism and external environmental insult highlights the need for future work with other polymerase-lesion combinations to fully understand damage-induced replication infidelity.

Mismatch Extension and Proofreading

DNA polymerases extend mismatched primer termini less efficiently than matched primer. This is expected given that incorporation involves in-line nucleophilic attack of the 3′-OH of the primer and given that the nascent base pair binding pocket is partly defined by the primer-terminal base pair (Fig. 2). The extent of discrimination is mismatch-specific (33), with certain mismatched termini (*e.g.* G-T) more readily extended than others (*e.g.* purine-purine mismatches). Certain polymerases like Pol ζ and Pol κ are reported to be particularly promiscuous at mismatch extension (10), which may reflect their special roles in extending damaged primer-templates following incorporation opposite a lesion by another polymerase (10). Other polymerases discriminate between correct and incorrect termini by factors exceeding 10,000-fold (33), providing the opportunity to proofread. For polymerases with intrinsic proofreading activity, slow mismatch extension allows the primer terminus to fray and partition to the exonuclease active site to allow excision, and the balance between mismatch extension and excision determines the contribution of proofreading to fidelity (15, 33, 34). This balance can be perturbed by certain amino acid replacements at either of the two active sites or even between them (references in Ref. 15) or by increasing the dNTP concentration to shift partitioning in favor of polymerization (for further discussions and structural perspectives, see Refs. 15, 33, and 34). Although many (*e.g.* at least 10 of 15 template-dependent human) polymerases lack intrinsic proofreading activity (2, 3), it is possible that dissociation from DNA after misinsertion may allow proofreading by the exonuclease activity intrinsic to another replication or repair protein, such as Pol δ, Pol ϵ, or apurinic/apyrimidinic endonuclease (50). For example, extrinsic exonucleolytic proofreading could improve the fidelity of Pol α (51) during initiation of Okazaki fragments, the fidelity of Pol η at a replication fork (52), or the fidelity of Pol β during single-nucleotide BER (53). Accessory proteins other than exonucleases have also been demonstrated to modulate the fidelity of DNA synthesis (reviewed in Ref. 15, and see Ref. 54 and references therein).

Substrate Misalignments and Insertion/Deletion Fidelity

DNA synthesis errors include insertion or deletion of bases resulting from strand misalignment (55). As for base substitutions, insertion/deletion error rates vary widely in a polymerase- and DNA sequence-dependent manner (56, 57), such that single base deletion error rates (Fig. 1, *bottom*) can sometimes exceed base substitution error rates (58). Misalignments with unpaired bases in the template strand result in deletions, whereas unpaired bases in the primer strand yield additions. Slippage probability may be modulated by fraying during polymerase translocation or during cycles of polymerase dissociation/association with the primer-template (15, 57). Single base deletions can also result from misinsertion of a base followed by primer relocation to convert the mismatched terminus into a matched terminus with an unpaired template base in the upstream duplex. Insertion/deletion errors

may also be initiated by misalignment in the active site (*e.g.* see Fig. 2*C*) when an incoming dNTP forms a correct Watson-Crick base pair but with the wrong template base. Primer relocation and active site misalignment can both result in primer termini with one or more correct base pairs, thereby allowing more efficient polymerization following insertion of an incorrect nucleotide or insertion opposite a lesion (Refs. 15, 56, 57, 59 and references therein). Transient misalignment can also yield substitution errors at very high rates by a dislocation process in which misalignment is followed by correct insertion and then realignment and mismatch extension (56). When strand misalignments occur in repetitive sequences, the unpaired base(s) can be present at some distance from the polymerase active site and the misaligned intermediate can be stabilized by correct base pairs whose number increases with increasing repeat sequence length (55). Thus, long repetitive sequences can provide stable misaligned intermediates that favor polymerization over proofreading. This explains why the insertion/deletion error rates of most polymerases increase with increasing repeat sequence length and why even proofreading-proficient replicative DNA polymerases with very high base substitution fidelity have low single base deletion fidelity (*e.g.* Fig. 1, *bottom*) when copying long homopolymeric sequences (*e.g.* Refs. 55 and 60 and references therein). That such low insertion/deletion fidelity occurs during replication *in vivo* is clearly indicated by the high level of genome-wide repeat sequence (microsatellite) instability observed in cells lacking the ability to correct replication errors by mismatch repair. Insertion/deletion errors are not limited to small numbers of nucleotides. During DNA synthesis between distant direct and inverted repeats, DNA polymerases can also generate simple and complex insertion/deletions involving hundreds of nucleotides. A more extensive discussion of insertion and deletion errors generated during DNA synthesis can be found in Refs. 55 and 56 with structural perspectives in Ref. 15. A better understanding of replication fidelity for insertion/deletion errors should improve an understanding of the relationship between repetitive DNA sequence instability and various types of cancer, neurodegenerative diseases, and phase variation at contingency loci in pathogenic organisms.

Acknowledgments—I sincerely thank Katarzyna Bebenek and William A. Beard for thoughtful discussions, several great suggestions, and critical reading of this manuscript.

REFERENCES

1. Watson, J. D., and Crick, F. H. C. (1953) *Nature* **171,** 737–738
2. Hübscher, U., Maga, G., and Spadari, S. (2002) *Annu. Rev. Biochem.* **71,** 133–163
3. Shcherbakova, P. V., Bebenek, K., and Kunkel, T. A. (2003) *Sci. Aging Knowl. Environ.* sageke.sciencemag.org/cgi/content/full/sageke;2003/8/ref31
4. Schaaper, R. M. (1993) *J. Biol. Chem.* **268,** 23762–23765
5. Loeb, L. A. (2003) *Cancer Res.* **51,** 3075–3079
6. Friedberg, E. C., Walker, G. C., and Siede, W. (1995) *DNA Repair and Mutagenesis*, American Society for Microbiology, Washington, D. C.
7. Goodman, M. F. (2002) *Annu. Rev. Biochem.* **71,** 17–50
8. Kunkel, T. A., Pavlov, Y. I., and Benenek, K. (2003) *DNA Repair* **2,** 135–149
9. Friedberg, E. C., Wagner, R., and Radman, M. (2002) *Science* **296,** 1627–1630
10. Prakash, S., and Prakash, L. (2002) *Genes Dev.* **16,** 1872–1883
11. Livneh, Z. (2001) *J. Biol. Chem.* **276,** 25639–25642
12. Tissier, A., McDonald, J. P., Frank, E. G., and Woodgate, R. (2000) *Genes Dev.* **14,** 1642–1650
13. Zhang, Y., Yuan, F., Wu, X., and Wang, Z. (2000) *Mol. Cell. Biol.* **20,** 7099–7108
14. Johnson, R. E., Washington, M. T., Haracska, L., Prakash, S., and Prakash, L. (2000) *Nature* **406,** 1015–1019
15. Kunkel, T. A., and Bebenek, K. (2000) *Annu. Rev. Biochem.* **69,** 497–529
16. Beard, W. A., and Wilson, S. H. (1998) *Chem. Biol.* **5,** R7–R13
17. Steitz, T. A. (1999) *J. Biol. Chem.* **274,** 17395–17398
18. Doublié, S., Sawaya, M. R., and Ellenberger, T. (1999) *Structure* **7,** R31–R35
19. Beard, W. A., and Wilson, S. H. (2003) *Structure* **11,** 489–496
20. Friedberg, E. C., Fischhaber, P. L., and Kisker, C. (2001) *Cell* **107,** 9–12
21. Beard, W. A., and Wilson, S. H. (2001) *Structure* **9,** 759–764
22. Garcia-Diaz, M., Bebenek, K., Krahn, J. M., Blanco, L., Kunkel, T. A., and Pedersen, L. (2004) *Mol. Cell*, **13,** 561–572
23. Steitz, T. A., Smerdon, S. J., Jager, J., and Joyce, C. M. (1994) *Science* **266,** 2022–2025
24. Kool, E. T. (2002) *Annu. Rev. Biochem.* **71,** 191–219
25. Loeb, L. A., and Kunkel, T. A. (1982) *Annu. Rev. Biochem.* **51,** 429–457
26. Boudsocq, F., Ling, H., Yang, W., and Woodgate, R. (2002) *DNA Repair* **1,** 343–358
27. Ling, H., Boudsocq, F., Woodgate, R., and Yang, W. (2001) *Cell* **107,** 91–102
28. Ling, H., Boudsocq, F., Plosky, B. S., Woodgate, R., and Yang, W. (2003) *Nature* **424,** 1083–1087
29. Washington, M. T., Helquist, S. A., Kool, E. T., Prakash, L., and Prakash, S. (2003) *Mol. Cell. Biol.* **23,** 5107–5112
30. Petruska, J., Goodman, M. F., Boosalis, M. S., Sowers, L. C., Cheong, C., and Tinoco, I., Jr. (1988) *Proc. Natl. Acad. Sci. U. S. A.* **85,** 6252–6256
31. Echols, H., and Goodman, M. F. (1991) *Annu. Rev. Biochem.* **60,** 477–511
32. Kool, E. T. (1998) *Biopolymers* **48,** 3–17
33. Goodman, M. F., Creighton, S., Bloom, L. B., and Petruska, J. (1993) *Crit. Rev. Biochem. Mol. Biol.* **28,** 83–126
34. Johnson, K. A. (1993) *Annu. Rev. Biochem.* **62,** 685–713
35. Showalter, A. K., and Tsai, M.-D. (2002) *Biochemistry* **41,** 10571–10576
36. Beard, W. A., Shock, D. D., Vande Berg, B. J., and Wilson, S. H. (2002) *J. Biol. Chem.* **277,** 47393–47398
37. Vande Berg, B. J., Beard, W. A., and Wilson, S. H. (2001) *J. Biol. Chem.* **276,** 3408–3416
38. Arndt, J. W., Gong, W., Zhong, X., Showalter, A. K., Liu, J., Dunlap, C. A., Lin, Z., Paxson, C., Tsai, M.-D., and Chan, M. K. (2001) *Biochemistry* **40,** 5368–5375
39. Yang, L., Beard, W. A., Wilson, S. H., Broyde, S., and Schlick, T. (2002) *J. Mol. Biol.* **317,** 679–699
40. Washington, M. T., Prakash, L., and Prakash, S. (2001) *Cell* **107,** 917–927
41. Purohit, V., Grindley, N. D. F., and Joyce, C. M. (2003) *Biochemistry* **42,** 10200–10211
42. Post, C. B., and Ray, W. J., Jr.(1995) *Biochemistry* **34,** 15881–15885
43. Minnick, D. T., Liu, L., Grindley, N. D. F., Kunkel, T. A., and Joyce, C. J. (2002) *Proc. Natl. Acad. Sci. U. S. A.* **99,** 1194–1199
44. Grollman, A. P., and Moriya, M. (1993) *Trends Genet.* **9,** 246–249
45. Fowler, R. G., and Schaaper, R. M. (1997) *FEMS Microbiol. Rev.* **21,** 43–54
46. Krahn, J. M., Beard, W. A., Miller, H., Grollman, A. P., and Wilson, S. H. (2003) *Structure* **11,** 121–127
47. McCulloch, S. D., Kokoska, R. J., Masutani, C., Iwai, S., Hanaoka, F., and Kunkel, T. A. (2004) *Nature*, **428,** 97–100
48. Yang, I.-Y., Miller, H., Wang, Z., Frank, E. G., Ohmori, H., Hanaoka, F., and Moriya, M. (2003) *J. Biol. Chem.* **278,** 13989–13994
49. Perrino, F. W., Blans, P., Harvey, S., Gelhaus, S. L., McGrath, C., Akman, S. A., Jenkins, G. S., LaCourse, W. R., and Fishbein, J. C. (2003) *Chem. Res. Toxicol.* **16,** 1616–1623
50. Chou, K. M., and Cheng, Y. C. (2002) *Nature* **415,** 655–659
51. Perrino, F. W., and Loeb, L. A. (1990) *Biochemistry* **29,** 5226–5231
52. Bebenek, K., Matsuda, T., Masutani, C., Hanaoka, F., and Kunkel, T. A. (2001) *J. Biol. Chem.* **276,** 2317–2320
53. Matsuda, T., Vande Berg, B. J., Bebenek, K., Osheroff, W. P., Wilson, S. H., and Kunkel, T. A. (2003) *J. Biol. Chem.* **278,** 25947–25951
54. Bebenek, A., Carver, G. T., Kloos Dressman, H., Kadyrov, F. A., Haseman, J. K., Petrov, V., Konigsberg, W. H., Karam, J. D., and Drake, J. W. (2002) *Genetics* **162,** 1003–1018
55. Streisinger, G., Okada, Y., Emrich, J., Newton, J., Tsugita, A., Terzaghi, E., and Inouye, M. (1966) *Cold Spring Harbor Symp. Quant. Biol.* **31,** 77–84
56. Kunkel, T. A. (1990) *Biochemistry* **29,** 8003–8011
57. Bebenek, K., and Kunkel, T. A. (2000) *Cold Spring Harbor Symp. Quant. Biol.* **65,** 81–91
58. Bebenek, K., García-Díaz, M., Blanco, L., and Kunkel, T. A. (2003) *J. Biol. Chem.* **278,** 34685–34690
59. Pagès, V., and Fuchs, R. P. (2003) *Science* **300,** 1300–1303
60. Longley, M. J., Nguyen, D., Kunkel, T. A., and Copeland, W. C. (2001) *J. Biol. Chem.* **276,** 38555–38562

DNA Replication Fidelity

Thomas A. Kunkel

J. Biol. Chem. 2004, 279:16895-16898.
doi: 10.1074/jbc.R400006200 originally published online February 26, 2004
