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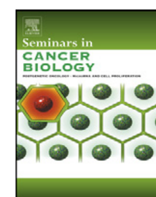

Review

Mutator phenotypes due to DNA replication infidelity

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ABSTRACT

This article considers the fidelity of DNA replication performed by eukaryotic DNA polymerases involved in replicating the nuclear genome. DNA replication fidelity can vary widely depending on the DNA polymerase, the composition of the error, the flanking sequence, the presence of DNA damage and the ability to correct errors. As a consequence, defects in processes that determine DNA replication fidelity can confer strong mutator phenotypes whose specificity can help determine the molecular nature of the defect.

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1. Introduction

The fidelity with which genetic information is replicated depends on the ability of DNA polymerases to select correct nucleotides rather than incorrect or damaged nucleotides for incorporation, without adding or deleting nucleotides. Polymerase selectivity is a major determinant of fidelity both at the replication fork and during synthesis to repair DNA damage. Mismatches generated during DNA chain elongation can be removed by 3′-exonuclease activity of the major replicative polymerases, thereby enhancing fidelity. If a mismatch escapes proofreading, DNA mismatch repair (MMR) can excise the replication error in the nascent strand and replace it with the correct sequence. Under normal circumstances, nucleotide selectivity, proofreading and MMR operate in series to replicate the genome with very high fidelity, thereby contributing to low spontaneous mutation rates (Fig. 1). Consequently, defects in any of these three processes can increase mutation rates, and this mutator phenotype can potentially be a driving force for cancer.

When lesions in DNA generated by endogenous cellular metabolism or exposure to chemical or physical insults from the external environment are not removed prior to replication, they sometimes distort the DNA helix and impede replication fork progression. In such circumstances, cell survival can be enhanced by several different DNA transactions. One such transaction is translesion synthesis (TLS), a process that allows lesions to be tolerated until they can be repaired. TLS is catalyzed by highly specialized, exonuclease-deficient DNA polymerases whose catalytic properties, including fidelity, are quite different than those that perform the bulk of replication. This review focuses on the eukaryotic replicative and TLS DNA polymerases that have critical roles in accurately and efficiently replicating the nuclear genome. Readers interested in DNA synthesis catalyzed in mitochondria, or in additional DNA polymerases that function in DNA repair, can consult other reviews [1–4]. Emphasis here is on the fidelity of replication, how it can be reduced to result in mutator phenotypes associated with cancer, and differences in replication error specificity that may have diagnostic value when considering replication infidelity as a source of point mutations arising in tumor cells.

2. Multiple DNA polymerases and their functions

DNA polymerases are classified by sequence homology into seven families (A, B, C, D, X, Y and RT). Most organisms encode multiple polymerases, often including several members of the same family. The human genome encodes 16 DNA polymerases, and more than half are involved in replicating the nuclear genome (Table 1). Four (Pols α, δ, ε and ζ) are B family members, four (Pols η, κ, ι and Rev1) are Y family members; two (Pols θ and ν) are A family members. These enzymes can have multiple functions, and some uncertainty remains as to exactly where and when they operate *in vivo*. Nonetheless, their primary functions are currently thought to be in replication and TLS (Table 1).

2.1. The major replicative DNA polymerases

Pols α, δ and ε perform the vast majority of nuclear DNA replication. Several models have been put forth for their division of labor

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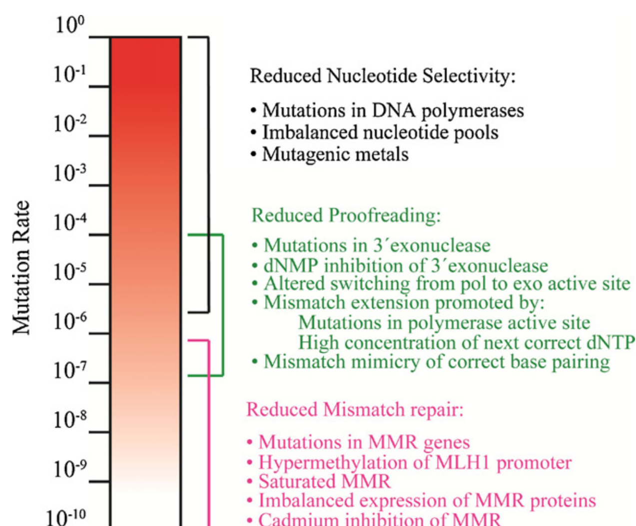

Fig. 1. Contribution of nucleotide selectivity, proofreading and DNA mismatch repair to DNA replication fidelity. The figure depicts the wide-ranging contributions of three major processes that act in series to determine DNA replication fidelity. The colored brackets illustrate the investment each process makes to the overall fidelity. Conditions that comprise each process are shown on the right.

at the nuclear DNA replication fork [5,6]. These models all share the idea that initiation of replication at origins and of each Okazaki fragment on the lagging strand template requires the RNA primase activity associated with Pol α to synthesize RNA primers of ~10 bases (Fig. 2A). Pol α then extends these primers by incorporating about 20–30 deoxynucleotides. Once DNA chains are initiated, current evidence [5,7] suggests that the leading strand template may be copied primarily by Pol ε, a highly processive enzyme with an associated proofreading exonuclease activity. Pol δ copies primarily the lagging strand template, generating a series of Okazaki fragments of approximately 200–300 base pairs each that are ultimately processed to remove RNA primers and permit ligation [8].

2.2. The TLS polymerases

Although the above situation may apply to replicating undamaged DNA, enzymology becomes more complicated when the fork encounters lesions that distort the DNA helix (Fig. 2B). Family B members like Pols α, δ and ε depend heavily on normal helix geometry for efficient and accurate synthesis [1,9], such that helix distorting lesions can slow or prevent replication fork progression. To solve this problem, a stalled replication fork can elicit one or more switches among DNA polymerases capable of bypassing lesions. The specialized TLS polymerases include Pols ζ, η, κ, ι and Rev1 (Y family) and Pols θ and ν (A family). These polymerases can incorporate nucleotides opposite lesions and/or extend the resulting primer terminus for one or more nucleotides, thus creating primer-templates that can be used by the major replication enzymes [10,11]. The number of switches involved in TLS, and the identity and number of polymerases required, can vary depending on the lesion, of which there are many types that differ by composition and structure [12]. The number of switches also depends on the substrate preferences of the various polymerases, which also vary widely and can partially overlap. The location and timing of TLS may vary, sometimes occurring at the fork during ongoing DNA replication, sometimes occurring during post-replication gap-filling synthesis, e.g., catalyzed by Pol ζ [13], or perhaps occurring during excision repair (e.g., Pol κ). In fact, eukaryotic DNA polymerases other than those listed in Table 1 also have been implicated in TLS, including two family X members Pol β and Pol λ that fill short gaps during base excision repair and non-homologous end joining of double strand breaks in DNA. Pol β has been shown to be involved with bypass of an abasic site and a d(GpG)-cisplatin adduct [14,15] and PCNA was found to efficiently stimulate the bypass of an abasic site by Pol λ [2,16,17]. Readers interested in the substrate specificities of the TLS polymerases and mechanisms of polymerase switching involving post-translational modifications of polymerases and their accessory proteins can consult any of several recent reviews on this topic [4,18,19].

3. The fidelity of DNA synthesis

The potential of replication infidelity to drive cancer via a mutator phenotype may depend heavily on the enzymatic source and the specificity of DNA biosynthetic errors. Studies of DNA synthesis fidelity *in vitro* reveal wide variations in error rates for the two main types of errors that DNA polymerases generate, single base pair substitutions and single base deletions (Fig. 3). These rates reflect nucleotide selectivity, which prevents errors from forming, and also exonucleolytic proofreading, which corrects mismatches during ongoing replication.

3.1. Nucleotide selectivity/error prevention

Most DNA polymerases lack intrinsic 3′-exonuclease activity to excise errors. Therefore, their fidelity depends on the ability to prevent incorporation of incorrect dNTPs that lead to base substitutions, and to prevent incorporation involving misaligned substrates that leads to loss or addition of nucleotides. Amazingly, DNA polymerase selectivity can vary over a million-fold range (Fig. 1).

3.1.1. Major replicative polymerases

Pols α, δ and ε nearly always insert correct dNTPs onto properly aligned primer-templates. This is illustrated by the low single base substitution and deletion error rates of Pols α, δ and ε. These error

Table 1
Human DNA template-dependent DNA polymerases.

DNA polymerase	Family	Catalytic subunit				3′ to 5′ Exonuclease	Proposed
		Mass (kDa)	Human gene	Location	Yeast *(Sc)* gene		Primary function
α (alpha)	B	165	*POLA*	Xp22.1-p21.3	*POL1 (CDC17)*	No (Primase)	Okazaki fragment initiation
δ (delta)	B	125	*POLD 1*	19q13.3	*POL3 (CDC2)*	Yes	Lagging strand replication
ε (epsilon)	B	255	*POLE*	12q24.3	*POL2*	Yes	Leading strand replication
ξ (zeta)	B	353	*POLZ (REV3)*	6q21	*REV3*	No	Translesion synthesis, SHM
η (eta)	Y	78	*POLH (RAD30, RAD30A, XPV)*	6p21.1	*RAD30*	No	Translesion synthesis SHM
ι (iota)	Y	80	*POLI (RAD30B)*	18q21.1	none	No	Translesion synthesis, SHM?
κ (kappa)	Y	76	*POLK (DINB1)*	5q13	none	No	Translesion synthesis
ν (nu)	A	100	*POLN*	4p16.3	none	No	Translesion synthesis?
θ (theta)	A	198	*POLNQ*	3q13.3	none	No	Translesion synthesis, SHM?

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