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Eukaryotic Translesion Polymerases and Their Roles and Regulation in DNA Damage Tolerance

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INTRODUCTION

The faithful replication of DNA and proper transmission of chromosomes are essential for inheritance of an accurate and complete genome, which encodes the information necessary for life. Ironically, the process of living itself generates reactive metabolites that can cause DNA damage. Cells are also exposed to a vast array of exogenous stresses that can directly or indirectly lead to DNA damage. Although cells contain multiple, highly complex systems to faithfully restore DNA to its original sequence and structure, at times distinct mechanisms are required to temporarily tolerate DNA damage without mediating repair of a lesion. These DNA damage tolerance processes contribute to survival after DNA damage and, in some situations, also actively promote the generation of mutations. The factors responsible for spontaneous and damage-

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induced mutagenesis are now known to include specialized DNA polymerases, termed translesion polymerases, that are found in all domains of life. Understanding of these potentially mutagenic yet highly conserved polymerases is critical to a complete knowledge of cell stress responses, mechanisms of genomic integrity, cell death after DNA damage, induction of mutations, disease development, and the processes of adaptation and evolution.

Here we will briefly introduce the many strategies a cell may employ to allow survival in the face of DNA damage before we turn to the contribution of damage tolerance mechanisms, in particular translesion synthesis (TLS). We describe the DNA polymerases that mediate TLS and highlight the unique properties of the Rev1 and Pol ζ families, which are together responsible for the majority of mutations in eukaryotes from yeast to humans. We review our current understanding of the eukaryotic translesion polymerases and emphasize the complex regulation that utilizes mutagenesis for a cell's benefit while preventing rampant mutations under normal conditions. We conclude with a discussion of the two major models for the regulation of mutagenesis resulting from TLS.

DNA REPAIR AND TOLERANCE

DNA damage is a highly complex cellular insult and represents a major obstacle to proper cellular functions. DNA damage can lead to cell death or, alternatively, diseases in which damaged cells fail to die, such as cancer. DNA lesions and strand breaks interfere with replication, potentially causing mutations, and also hinder transcription, affecting gene expression and cellular physiology. Compounding the challenge for the cell, DNA damage is also extremely prevalent. Approximately 30,000 lesions are generated spontaneously in a mammalian cell per day (146). Major sources of spontaneous DNA damage include reactive oxygen species produced primarily during aerobic metabolism; base deamination, especially of cytosine to uracil; and the inherent susceptibility of DNA to depurinations and depyrimidinations (53, 146). Additionally, many environmental factors can cause DNA damage, such as ionizing or UV radiation and chemical agents, including methyl methanesulfonate, cisplatin, and benzo[*a*]pyrene (53). These agents can cause modifications of the nitrogenous bases or breaks in the sugar-phosphate backbone.

The wide variety of DNA lesions that result from diverse DNA-damaging agents has necessitated the evolution of a multitude of cellular responses to DNA damage (Fig. 1A). These DNA repair pathways consist of systems that directly reverse the damage and several types of excision repair: nucleotide excision repair, base excision repair, and mismatch repair. Additional mechanisms of DNA repair include single-strand break repair and the repair of double-strand breaks by nonhomologous end joining, homologous recombination, or single-strand annealing. The reader is referred to reference 53 and the many excellent reviews that are available for further information on DNA repair.

Additionally, cells possess mechanisms to temporarily tolerate DNA damage until DNA repair processes can remove the damage (Fig. 1A). In eukaryotes, tolerance includes an error-free pathway and a parallel, more mutagenic pathway, as reviewed by Andersen et al. (7). The type of posttranslational

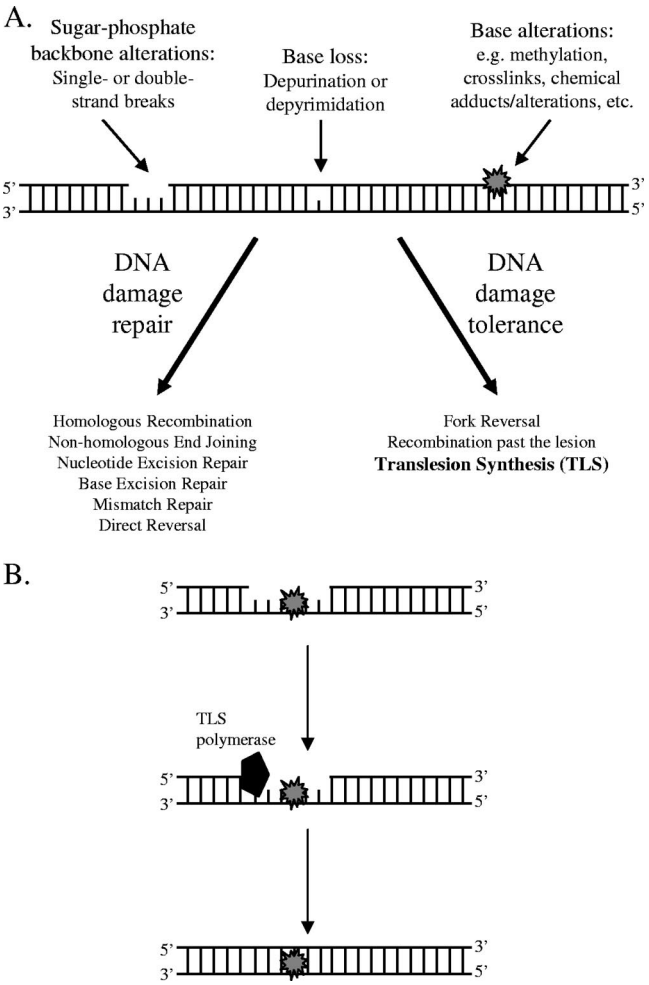

FIG. 1. DNA damage repair and bypass mechanisms. (A) DNA damage results in breakage of the sugar-phosphate backbone, DNA base loss (indicated by a gap in the DNA), or base alterations (as indicated by the gray star). This damage can be repaired/removed from the DNA strand or tolerated, in which case the DNA lesion remains but cellular processes continue. (B) An example of the DNA damage tolerance mechanism TLS, whereby a damaged DNA template is replicated using a TLS polymerase and the damage remains in the genome. A more detailed mechanism of TLS is described in the text and represented in Fig. 4.

modification on the processivity clamp proliferating cell nuclear antigen (PCNA) plays a major role in determining the tolerance pathway utilized. Part of the tolerance to DNA damage lies in the ability of cells to replicate across damaged DNA, a process called TLS that is a major component of the more mutagenic branch of tolerance. Without DNA damage tolerance, cells face the risk of replication fork collapse, translocations, chromosome aberrations, and cell death.

Conceptually, DNA damage tolerance is quite different from DNA repair in that, rather than restoring DNA to its proper sequence and structure, the lesion is still present in the DNA after DNA damage tolerance pathways act (Fig. 1B) (53). Since the function of damage tolerance is to temporarily bypass a DNA lesion rather than to regenerate the original sequence, damage tolerance mechanisms are optimized to allow survival by promoting the completion of DNA replication

TABLE 1. Genes encoding catalytic subunits of eukaryotic DNA translesion polymerases

Polymerase	Gene in:				
	S. cerevisiae	*S. pombe*	*D. melanogaster*	Mouse	Human
Pol ζ	*REV3*	*rev3*$^+$	*mus205/dmREV3*	*Rev3*	*REV3L*
Rev1	*REV1*	*rev1*$^+$	*rev1*	*Rev1*	*REV1*
Pol κ		*dinB*$^+$*/mug40*$^+$		*Polκ/DinB1*	*DINB1*
Pol η	*RAD30*	*eso1*$^{+a}$	*DNApol-η*	*Polη*	*RAD30A/XPV*
Pol ι			*DNApol-ι*	*Polι*	*RAD30B*

[a] *S. pombe eso1*$^+$ contains two separable protein domains. The amino-terminal end is homologous to Pol η and exhibits in vivo phenotypes and in vitro activities similar to those of Pol η homologs in other organisms (152, 241). The carboxy-terminal end is comprised of an essential sister chromatid cohesion protein (152).

rather than protecting the accuracy of the genomic information. Therefore, it is not surprising that DNA damage tolerance often operates in a mutagenic manner. In this review, we focus on the molecular mechanisms behind the generation of mutations by DNA damage tolerance and how these potentially mutagenic pathways are exquisitely regulated to promote survival while restricting the introduction of mutations. Another consequence of the complex regulatory pathways is that the mutations which do arise occur under conditions of stress when they might be evolutionarily advantageous through increasing genetic variability, as demonstrated in somatic hypermutation (SHM) of immunoglobulin genes.

TLS

TLS is the process by which a DNA lesion is bypassed by the incorporation of a nucleotide opposite to the lesion (53) (Fig. 1B). Many DNA lesions cannot be used as a template by the highly stringent replicative DNA polymerases, which are optimized to replicate the entire genome with high accuracy and efficiency (15, 53). However, a class of DNA polymerases with particular characteristics, termed TLS polymerases, can use damaged DNA as templates and insert nucleotides opposite lesions, despite the conformational constraints that many modified bases may impose (53, 68, 217). TLS polymerases are found in organisms throughout all three domains of life. Most TLS polymerases are members of the Y family of DNA polymerases (199), a unique class of DNA polymerases with specialized structures optimized to allow replication on damaged DNA substrates and, in some cases, to promote mutagenic DNA synthesis. Additionally, other classes of DNA polymerases, such as the A and X families, can exhibit TLS activity, but as this activity is often weak or not the primary function of these polymerases (see below), we focus on the Y family of DNA polymerases, which are uniquely adapted for TLS. The Y family members include Rev1, Pol κ (DNA Pol IV in bacteria), Pol η, Pol ι, and bacterial DNA Pol V (UmuD′$_2$C). For historical reasons, each polymerase has multiple names, resulting from genetic or biochemical characterizations carried out over many years using different organisms. Since these names are used interchangeably in the literature, additional names for polymerases are indicated in the section titles and in Table 1. Another eukaryotic DNA polymerase, Pol ζ, is a member of the B family of DNA polymerases, which includes replicative DNA polymerases, yet it is capable of TLS and has a specialized ability to extend from mismatched and/or distorted primer-template pairs, including those opposite to DNA lesions, with remarkably high efficiency compared to most other polymerases.

Discovery and History of Translesion Polymerases

Genes encoding translesion polymerases have been known for decades; however, their function remained mysterious until relatively recently. In 1971, Jeffrey Lemontt isolated genes actively involved in the process of mutagenesis by screening for reversionless mutants of *Saccharomyces cerevisiae* that were unable to revert an auxotrophic marker to the wild-type allele after UV irradiation (137). Using this approach, *REV1* (encoding the Rev1 DNA polymerase) and *REV3* (encoding the catalytic subunit of Pol ζ) were identified as genes that when mutated conferred a strikingly lower frequency of mutations than the wild-type strain. A conceptually analogous screen for unmutable genes in *Escherichia coli* led to the identification of *umuC* (encoding the catalytic subunit of UmuD′$_2$C, DNA Pol V) (109).

Although the *REV1*, *REV3*, and *umuC* genes were identified by their profound contributions to damage-induced mutagenesis, other translesion polymerase genes have more subtle effects on mutagenesis and were first identified primarily by homology searches with other TLS polymerases. For example, *RAD30* and Pol ι (*hRAD30B*) were first identified solely by their homology to the TLS polymerase genes *REV1*, *umuC*, and *dinB* (initially identified in *E. coli*) (112, 165, 166, 225, 251). It was not until 1996 that the first biochemical description of a specialized translesion polymerase appeared (Pol ζ, a B family DNA polymerase [185]), followed rapidly by the demonstration that the Rev1 protein had a restricted DNA polymerase activity and was able to insert Cs opposite an abasic site (184). Even then, it was not until 1999, with the characterization of the translesion polymerase activity of DNA polymerase η (100, 156, 157), that it was recognized that all of the genes which shared homology with the eukaryotic *REV1* and bacterial *umuC* were in fact genes for DNA polymerases with the unique ability to replicate over DNA lesions (extensively reviewed in references 68 and 217). This realization took so long in part because these novel translesion polymerases share almost no primary sequence homology with classical replicative DNA polymerases, and some have proved to be particularly difficult to purify. This new family of translesion DNA polymerases was named the Y family of DNA polymerases (199).

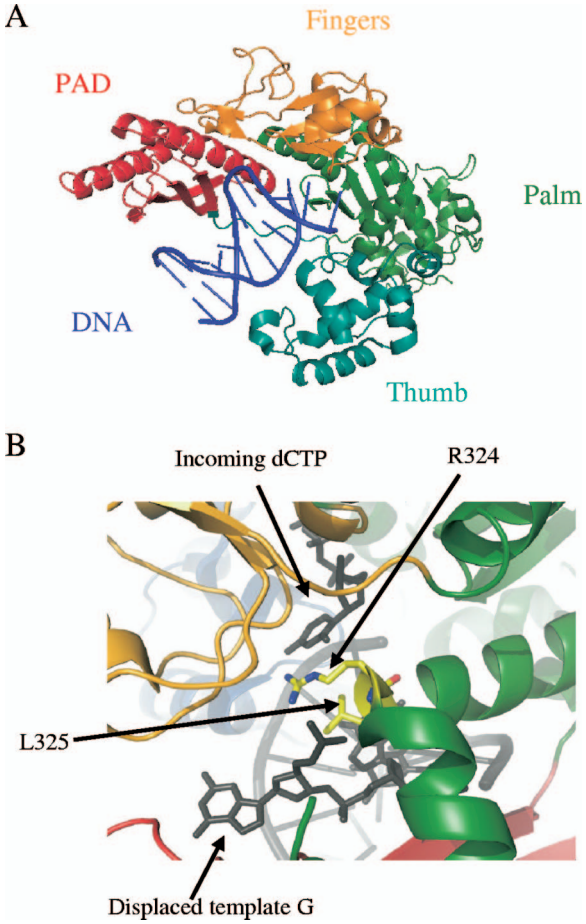

FIG. 2. Crystal structures of two Y family polymerases. (A) Co-crystal structure of the *S. cerevisiae* TLS Pol η with a DNA template containing a cisplatin cross-link. The structure is oriented to highlight the right-hand architecture as seen in both TLS and replicative polymerases. (Based on data from reference 6 and the RSCB protein data bank [PDB ID number 2r8j].) (B) Close-up view of the unique lesion bypass mechanism of Rev1 from *S. cerevisiae*. Highlighted are the novel leucine (L325) that helps to flip out the template guanine and the catalytic arginine (R324) that hydrogen bonds to stabilize the incoming dCTP. The domains of Rev1 are colored as in panel A, with the exception of the DNA, which is shown in black. (Based on data from reference 180 and the RCSB protein data bank [PDB ID number 2aq4].)

Physical Features of TLS Polymerases

Several seminal crystal structures provided initial insights into the architectural features that confer unique catalytic properties to the Y family members (147, 148, 180, 181, 232, 244, 245, 279), and recently many additional structures have been elucidated, which refine our understanding. Despite a nearly complete lack of primary sequence homology with all other known DNA polymerases, Y family members share the classic "right-hand" DNA polymerase fold (Fig. 2) (15, 217, 267). Like replicative polymerases, the catalytic aspartate and glutamate residues, which coordinate the divalent magnesium ions that stabilize the triphosphate group of the incoming deoxynucleoside triphosphate (dNTP), are located in the central palm region (15, 217, 266). The thumb and finger domains of Y family polymerases, analogous to those in replicative polymerases despite secondary structure variations, grip the DNA and make specific contacts with the primer and template strands, respectively (Fig. 2) (15, 217, 266).

Although they share a common overall architecture, Y family polymerases differ from replicative polymerases in certain key ways that allow them to perform TLS. At the domain level, Y family polymerases lack the intrinsic 3′-to-5′ exonuclease domain of replicative DNA polymerases that functions to proofread the newly replicated strand (68, 267). A novel little-finger domain, also called the polymerase-associated domain (PAD) (148, 232) or wrist (244), is present only in Y family polymerases and extends from the classical finger domain to make extra contacts with the DNA (Fig. 2) (266, 267). Certain TLS polymerases also contain additional regions, such as the "N-clasp" of DNA Pol κ, that further contribute to DNA binding (150). These additional DNA-binding regions provide important stability for the ternary complex, since Y family members have short, stubby thumb and finger domains which make few contacts with the DNA backbone (217, 266). Y family polymerases generally have an open grip on the DNA (Fig. 2) and a greatly reduced processivity relative to replicative DNA polymerases (55, 217); truncations of the little-finger domain or N clasp reduces DNA binding and processivity even further (148, 150, 217). Intriguingly, the little-finger domain (the least conserved region of the TLS polymerase domain) appears to contact the region of the template containing the lesion (Fig. 2) (160, 162) and has been implicated in lesion specificity (23).

Closer inspection of the active sites of Y family and replicative polymerases also reveals significant differences. Particularly for the archaeal and bacterial Y family polymerases, the active site is larger and more open than in other DNA polymerases (217, 266, 267). A more spacious active site allows accommodation of large bulky adducts (149, 180) and even two covalently linked bases in a thymine-thymine dimer (147). Other Y family members appear to have more constrained active sites that nonetheless are specialized to accommodate particular classes of DNA lesions (150). Further promoting their ability to use modified DNA templates, Y family polymerases make fewer contacts with the forming base pair (266, 267) and, in particular, lack the O helix of replicative DNA polymerases which, upon binding of a dNTP, rotates ~40° to sterically check the forming base pair (206). Based on crystallographic analysis, it has been proposed that some Y family polymerases may not exhibit an induced fit upon binding of the incoming dNTP, which contributes to the replicative fidelity of replicative polymerases (267); however, there is evidence to suggest a conformational change during catalysis by archaeal Dpo4, *S. cerevisiae* Pol η, and perhaps human Pol η as well (48, 102, 255).

As of the writing of this review, four eukaryotic Y family polymerases have been cocrystallized with DNA: human Pol ι (181), *S. cerevisiae* Pol η with a cisplatin adduct (Fig. 2A) (6), human Pol κ (150), and *S. cerevisiae* Rev1 (Fig. 2B) (179, 180). Each polymerase displays distinct and often unusual interactions with the DNA lesion and incoming nucleotide. For example, Rev1 uses an amino acid in the catalytic domain to base pair with an incoming dCTP in lieu of pairing with the DNA template (Fig. 2B) (180), while Pol ι appears to use an unusual Hoogsteen base pairing mechanism (181). In contrast, Pol κ

uses Watson-Crick base pairing to incorporate nucleotides and has a relatively constrained active site (150). Thus, although we have gained substantial insight at the molecular level into how Y family members are specialized to bypass DNA lesions, we still have much to learn about how the molecular architecture of each TLS polymerase active site helps it to achieve its bypass specificity.

TLS Polymerases Have Reduced Fidelity Relative to Replicative DNA Polymerases

The novel features of translesion polymerases that allow them to use an increased variety of altered DNAs as templates also confer decreased replication fidelity. Compared with replicative DNA polymerases, which utilize proofreading and exhibit error rates in the range of incorporating one incorrect nucleotide for every 10^6 to 10^8 bases replicated, TLS polymerases display error rates that can range from approximately one incorrect nucleotide for every 10 bases to one for every 10,000 bases when replicating undamaged DNA (68, 119, 217). Therefore, TLS polymerases have a potentially mutagenic activity inside the cell (52). The lack of a 3′-to-5′ proofreading domain reduces the fidelity of TLS polymerases operating on undamaged DNA by $\sim 10^{-2}$ compared to replicative DNA polymerases (68, 119, 267), and the limited number of contacts made with the template base and incoming nucleotide further decrease accuracy. Additionally, as mentioned above, it has been suggested that some TLS polymerases are less accurate because they do not undergo an induced fit upon nucleotide binding (266, 267), and certain TLS polymerases, like DNA Pol ι and Rev1, do not use canonical Watson-Crick base pairing (180, 217). Thus, as a consequence of their unusual polymerization mechanisms, TLS polymerases exhibit a markedly lower accuracy of base pair insertion on undamaged DNA templates relative to the replicative DNA polymerases.

Some TLS Polymerases Are Specialized for Replicating Cognate DNA Lesions or Particular DNA Substrates

However, despite their relatively low fidelity on undamaged DNA, a paradigm shift has reclassified TLS polymerases from generally being considered "error-prone" polymerases (68), as often initially described, to a more nuanced understanding of their role as lesion-specific bypass polymerases (52). It is now appreciated that certain TLS polymerases are optimized to efficiently replicate over particular DNA lesions, referred to as their cognate lesions, in a relatively accurate manner (97, 100, 253). Cognate lesions have been defined for several TLS polymerases by showing that the polymerase is able to bypass the lesion accurately in vitro and in vivo and that the efficiency of nucleotide insertion opposite to the lesion occurs with an efficiency equal to or higher than that on undamaged DNA (97, 100, 162, 253). This is strikingly seen in the case of DNA Pol η, which is specialized to bypass *cis-syn* TT dimers caused by UV irradiation (99, 100, 157). Although DNA Pol η exhibits among the lowest fidelities of any TLS polymerase on undamaged DNA ($\sim 10^{-1}$) (158), its highly accurate activity in bypassing this UV-induced lesion makes Pol η critical for the avoidance of sunlight-induced skin cancers in humans (discussed further below) (132). Additionally, Pol κ, and its archaeal and bacterial homologs, can bypass certain N^2-dG adducts accurately and efficiently (97).

EUKARYOTIC TRANSLESION POLYMERASES

Phylogenetic analysis and extensive biochemical characterization have revealed that there are five subfamilies within the Y family of DNA polymerases: Rev1, UmuC, DinB/Pol κ, Pol ι, and Pol η (199), each with their own unique enzymatic and physiological properties. Additionally, one non-Y family polymerase is required for the mutagenic bypass of DNA lesions in eukaryotes, DNA Pol ζ (Rev3/Rev7) (123). For this review, we will focus on the eukaryotic DNA polymerases involved in TLS. After highlighting the differing lesion bypass capabilities for each polymerase subfamily, including the accurate and efficient bypass of cognate lesions by some TLS polymerases, the mechanisms of regulation for expression and activity of each polymerase are reviewed.

Before fully discussing each eukaryotic TLS polymerase, we need to introduce one recurring theme for the regulation of eukaryotic TLS polymerases involving the physical and genetic interactions with PCNA and the proteins involved in modifying PCNA. The homotrimeric clamp, PCNA, serves as the processivity factor for Pols δ and ε during replication (26). For its role in DNA damage tolerance, particular ubiquitin modifications of PCNA are involved. Specifically, the Rad6-Rad18 complex catalyzes the monoubiquitination of PCNA at K164, a modification that stimulates TLS, the more mutagenic branch of tolerance (238). Monoubiquitination of PCNA can be later extended to polyubiquitination by the Mms2-Ubc13-Rad5 complex, which elicits an error-free mode of tolerance (7). In addition, attachment of SUMO (*s*mall *u*biquitin-related *mo*difier) at positions K164 and K127 of PCNA in *S. cerevisiae* has been found to affect phenotypes for DNA damage-induced survival as well as TLS-dependent mutagenesis in the absence of exogenous DNA damage (reviewed by Ulrich [246]). Therefore, the interaction(s) between TLS polymerases and PCNA is key in comprehending TLS activity and regulation, as discussed frequently in the sections below.

Rev1

Uniquely among eukaryotic Y family polymerases, Rev1 actively promotes the introduction of mutations in organisms ranging from unicellular yeast to multicellular organisms, including humans (65, 137). Cells bearing *rev1* mutations display a drastic reduction in spontaneous and induced mutagenesis by a wide variety of DNA-damaging agents (53, 123). In multiple genetic backgrounds and in response to different types of DNA lesions, mutations of *REV1* abolish most mutagenesis, indicating its fundamental importance to this biologically important process (123). For example, Rev1 is required for ~95% of all UV-induced base pair substitutions (124). Although only marginally correlated with the onset of cancer to date (85, 230), *REV1* has been shown to modulate the frequencies with which cisplatin-resistant cells are generated from an ovarian carcinoma cell line (144, 201). Therefore, *REV1* may contribute to cancer progression and could be an important target of cancer therapy.

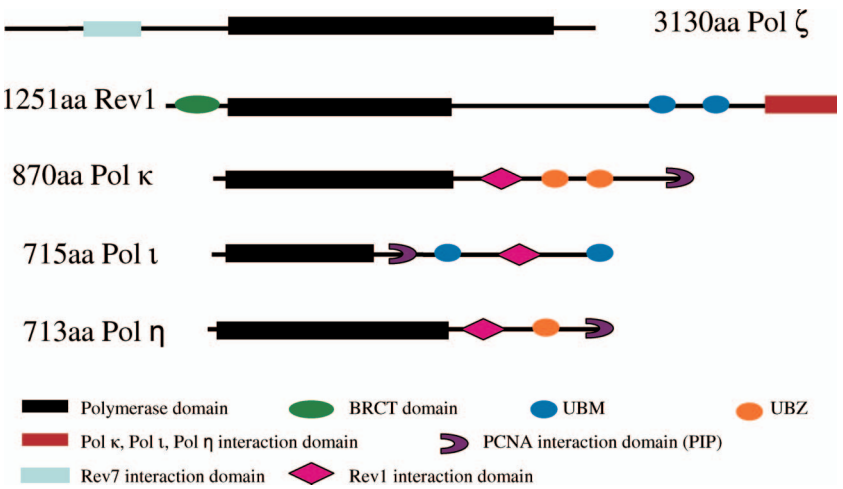

FIG. 3. Cartoon representation of the protein domains in the human B family TLS polymerase ζ and the Y family TLS polymerases Rev1, κ, ι, and η. aa, amino acids. (Based on data from references 58 and 268.)

Rev1's catalytic activity. Rev1 was the first member of the Y family to be shown to have the capability of catalyzing the formation of a phosphodiester bond (184). However, because its activity was limited, Rev1 was described as a DNA polymerase only after the discovery of the DNA polymerase activity of other Y family members (199). Rev1 has a polymerase activity that is restricted primarily to inserting dCMP nucleotides opposite template Gs and across from certain DNA lesions, such as abasic sites and adducted G residues (123, 184, 254). To accomplish this specificity, Rev1 uses a novel mechanism that selects dCTP as the incoming nucleotide by forming hydrogen bonds with a conserved arginine residue in the catalytic domain rather than by base pairing with the template base, as for all other known DNA polymerases (Fig. 2B) (180). Contacts are made between Rev1 and the template base to ensure its identity as a G, but the template base is flipped out of the active site by interactions with other conserved residues, allowing bypass of bulky G adducts (Fig. 2B) (180).

In contrast, a catalytically inactive mutant of Rev1 displays no reduction in levels of mutagenesis induced by a wide range of DNA-damaging agents, including UV light (80, 224), although a change in the mutation spectrum is observed (202, 224). Interestingly, DNA damage sensitivity and mutagenesis phenotypes are observable for the catalytic dead mutant after cells are exposed to 4-nitroquinoline 1-oxide, an alkylating agent that produces, among other lesions, N^2-dG adducts. The phenotypes are even more dramatic in the absence of error-free tolerance in *S. cerevisiae*, suggesting that the DNA polymerase activity is indeed important for the bypass of certain N^2-dG adducts (M. E. Wiltrout and G. Walker, unpublished data).

Rev1's noncatalytic function(s) and protein interactions. *REV1* is required for bypass of a 6-4 TT dimer in vivo, even though purified Rev1 is unable to insert a nucleotide opposite to UV photoproducts in vitro (183, 202, 276). Therefore, although Rev1's unique and highly specialized dCMP transferase catalytic activity is conserved from yeast to humans (142, 184), its DNA polymerase activity does not seem to be required for bypass of many lesions for which Rev1 function is required in vivo. Instead, the ability of Rev1 to confer resistance to DNA-damaging agents and promote mutagenesis results mainly from its interactions with other proteins, particularly other translesion DNA polymerases. Rev1 is notable among TLS polymerases for its multiple binding partners and possesses several protein-protein interaction modules, all of which are individually required for its function in vivo. These are the BRCT (*BR*CA1 *C-t*erminal) domain, the C-terminal ~100 amino acids, the PAD, and the ubiquitin-binding motifs (UBMs) (Fig. 3).

The N-terminal BRCT domain of Rev1 was the first region to be characterized, since the original loss-of-function *rev1-1* mutation in *S. cerevisiae*, whereby the *REV1* gene was identified, is located in the BRCT domain (65, 122, 137). The BRCT domain was initially characterized as an important motif in the BRCA1 breast cancer susceptibility protein and has subsequently been identified in a variety of proteins associated with cell cycle regulation and cellular responses to DNA damage (29, 249). In striking contrast to mutations in the catalytic active site, mutations affecting the BRCT domain largely inactivate Rev1 in vivo. In yeast, BRCT mutants exhibit a severe defect in survival and mutagenesis after DNA damage (137). More recently, mutations affecting the BRCT domain have also been shown to reduce *REV1* function in higher eukaryotes; however, the extent of the defect varies between studies (71, 96, 224). It was this finding that *REV1* function could be inactivated by a mutation which left the polymerase activity of Rev1 intact that first led Nelson et al. to propose a "second function" for Rev1 (183). This idea was supported by the recognition that BRCT domains can mediate protein-protein or protein-DNA interactions (29, 66, 115, 259). A model has subsequently been developed in which Rev1 mediates its function in survival and mutagenesis by recruiting and coordinating other DNA damage tolerance factors at the site of lesions rather than by bypassing DNA lesions directly (70, 80, 243).

Recently, the BRCT domain of Rev1 has been shown to interact with two DNA-binding proteins: the replicative clamp PCNA (71) and the Rev7 subunit of DNA Pol ζ (44a). Since a BRCT domain is not found in other TLS polymerases, these

interactions are likely to confer unique properties upon Rev1. It seems probable that the BRCT domain may promote a specialized interaction with damaged DNA to mark sites of incomplete replication that require TLS. Indeed, in subcellular localization studies, the BRCT domain is sufficient for nuclear localization (243) and is required for constitutive localization of Rev1 to replication foci (71). This may be because mouse Rev1 interacts with PCNA via the BRCT domain of Rev1 (71). Interestingly, Rev1 lacks the conserved PIP motif through which most proteins, including all of the other eukaryotic Y family polymerases, bind to PCNA (7). Thus, Rev1 likely interacts with a different surface of PCNA than the other TLS polymerases. As monoubiquitinated PCNA accumulates in response to agents that block replication forks (107), this unique interaction may have functional consequences for differential recruitment to lesions and/or, as one study indicates, stimulation of catalysis by Rev1 relative to Pol ζ (59). The biological relevance of stimulation of Rev1 catalysis by monoubiquitinated PCNA remains unresolved, though, since conflicting in vitro results have been reported (59, 82).

Moreover, as BRCT domains in other proteins have been found to interact with DNA at single-stranded regions or double-strand breaks (115, 259), the BRCT of Rev1 may also be directly involved in localizing Rev1 to aberrant DNA structures. Supporting this suggestion is a study demonstrating that both *S. cerevisiae* Pol ζ and Rev1 are recruited to the vicinity of an endonuclease-induced double-strand break (88). This property was found to require the Rev1 BRCT domain but not its catalytic activity.

In an activity unrelated to DNA binding, the BRCT domain of Rev1 may enable specific interactions with proteins phosphorylated by the DNA damage checkpoint kinase cascade. Tandem BRCT domains have been shown to interact preferentially with phosphorylated targets (66, 154, 270). Although Rev1 has only a single BRCT domain, it has also been implicated in phosphopeptide binding in vitro (270). To date, an interaction between the Rev1 BRCT domain and phosphorylated target proteins has not been demonstrated in vivo. In principle, however, the ability to bind phosphorylated target proteins would allow unique opportunities for regulation (or activity) of or by Rev1 relative to other TLS polymerases.

In addition to probable localization to DNA through interactions involving its BRCT domain, Rev1 interacts with, and may regulate, the activity of other TLS polymerases through its C terminus and PAD. The last ~100 amino acids of mammalian Rev1 interact with the TLS Pols η, ι, κ, and ζ (70, 176, 197, 243). Initially, the polymerase interaction region at the C terminus of Rev1 did not seem to be conserved between higher eukaryotes and yeast (107, 176, 243). However, extensive sequence alignment and functional studies have revealed that *S. cerevisiae* Rev1 does interact with another TLS polymerase, DNA Pol ζ, through its C terminus (2, 4, 44a, 44b, 117, 224). Beyond potentially regulating localization of TLS polymerases to DNA lesions, Rev1 can also affect the catalytic activity of other TLS polymerases in vitro, as in the case of its interaction with Rev3 that stimulates Pol ζ extension from a mismatch or opposite a DNA lesion (4). Importantly, mammalian and *S. cerevisiae rev1* constructs lacking this C-terminal polymerase interaction region are unable to complement a *rev1*Δ strain for survival or mutagenesis after DNA damage (4, 44b, 117, 122, 224), showing that Rev1 functions in vivo through interactions with other TLS polymerases. Additionally, in vitro, the PAD region of *S. cerevisiae* Rev1 interacts with the Rev7 subunit of DNA Pol ζ (2), as well as DNA Pol η, an interaction that mildly stimulates the polymerase activity of Rev1 (3).

Finally, mouse Rev1 binds ubiquitin via a noncanonical UBM (73). Interaction with ubiquitin is necessary for localization of Rev1 into DNA damage-induced foci (73) and for the hyperstimulation of its catalytic activity by PCNA-ubiquitin (261). Mutants with mutations in the UBM display increased chromosomal aberrations, decreased viability, and decreased mutagenesis after exposure to DNA-damaging agents (44b, 73, 261), showing that they, like the other interaction motifs, are required for *REV1* function in vivo. Murine Rev1 is monoubiquitinated itself, but the mechanism of ubiquitination, the position in the protein for this attachment, and the functional relevance of this modification remain unknown (73, 171).

Thus, multiple protein-protein interaction domains are critical for *REV1* function in vivo. These findings have led to a model in which Rev1 functions primarily as a scaffold for various postreplication repair proteins to localize mutagenic translesion complexes to sites of DNA damage and/or to modulate polymerase switching at the site of a DNA lesion (51, 132). Thus, Rev1 is thought to play a central role in TLS by regulating access of TLS polymerases to the primer terminus (51, 132).

Temporal and spatial regulation of Rev1. Despite its importance in regulating TLS, precisely how, when, and where Rev1 functions in vivo is not yet well understood. Rev1 clearly functions in mitotically dividing cells. The fact that the *REV1* transcript is upregulated during meiosis in *S. cerevisiae* (27, 37) and has the highest expression in human testis (176) suggests a meiotic function for Rev1 as well.

Although TLS is commonly considered to occur during replication/S phase at a stalled replication fork, recent evidence has led to the proposal that Rev1-dependent TLS acts after the replication machinery has reprimed downstream and generated a single-stranded DNA (ssDNA) gap opposite to a lesion. Strikingly, in *S. cerevisiae*, Rev1 levels fluctuate throughout the cell cycle and are maximal not during S phase, as might have been anticipated for a DNA polymerase, but rather during G_2 and throughout mitosis (257). *REV1* mRNA levels are cell cycle regulated to a lesser extent. Additionally, Rev1 is phosphorylated in a cell-cycle-dependent manner, as well as in response to DNA damage in *S. cerevisiae*, although how this affects Rev1 activity is not yet known (227). Together with a key study indicating that TLS can occur after replication in *S. cerevisiae* (151), this unexpected finding has led to a reevaluation of the implicit assumption that TLS polymerases act during replication to restart DNA synthesis by replacing the replicative DNA polymerase at stalled replication forks. Instead, one model is that Rev1 functions (primarily or in addition to during S phase) after the bulk of replication has been completed, binding to the aberrant primer termini located in gaps opposite DNA lesions (257). Although it appears that Rev1 is associated with chromatin constitutively throughout the cell cycle (227), Rev1 binds to ssDNA with high affinity and can likely translocate on this substrate to find primer termini (155). This ssDNA targeting may allow Rev1 to identify and localize to sites of incomplete replication opposite DNA lesions that

persist into late S/G_2/M. It could then be able to recruit Pol ζ, other TLS polymerases, or additional factors to bypass the lesion and fill in the ssDNA gap. In contrast to this evidence for a late S/G_2/M role for Rev1 in *S. cerevisiae*, *REV1* in DT40 cells is required for replication fork progression in the presence of DNA damage, indicating a role for Rev1 during S phase in this system (46). Taken together, these results suggest that the partitioning of Rev1 function between possible replicative and postreplicative roles may vary between biological systems.

Localization studies using ectopically overexpressed green fluorescent protein fusions have reported that Rev1 forms foci in vertebrate cells after DNA damage (71, 174, 175, 243). Damage-induced focus formation requires the UBMs (73), while the BRCT domain is sufficient for nuclear localization and basal focus formation but is not required for damage-induced focus formation (71, 243), highlighting the role of the protein-protein interactions in mediating Rev1 function. Under conditions of ectopic overexpression, colocalization of Rev1 foci with PCNA and Pol η has been interpreted to indicate that Rev1 associates with replication forks to enable continuous DNA synthesis on templates containing DNA lesions (71, 174, 243). This first led to a model in which Rev1 was thought to act mainly during replication (51, 132). However, Rev1 foci have also been observed in G_1 (175). Additionally, one study observed no Rev1 foci, occurring either spontaneously or after DNA damage, when a more physiological expression level of Rev1 was used (224). These authors propose that lack of focus formation reflects the need of the cell for only one or a small number of molecules of Rev1 at sites of stalled replication (224).

Given that the cell cycle regulation of Rev1 is likely to be complex and that cells appear to keep the levels of Rev1 as well as Pol ζ low (124), it seems likely that high levels of Rev1, especially during G_1 and S, would be detrimental. Additionally, Rev1 protein levels are under the control of proteasomal degradation throughout the cell cycle in *S. cerevisiae* (M. E. Wiltrout and G. Walker, unpublished data). Indeed, the fact that overexpressed Rev1 localizes to replication forks may help to explain why *S. cerevisiae* cells keep the level of Rev1 low during S phase. Even though overexpression of Rev1 in *S. cerevisiae* did not lead to any change in cell cycle length or the spontaneous mutation rate, most likely due to the multiple mechanisms regulating activity (124), future experiments taking advantage of new technology such as DNA combing may reveal phenotypes that are more challenging to observe. For example, DNA combing has been used to show that even mild overexpression of Pols β and κ in mammalian cells interferes with normal replication fork progression (212).

Potential relationship between diseases and proper Rev1 function. Novel in vivo functions for Rev1 are only beginning to be uncovered. In higher eukaryotes, additional pathways regulating Rev1/Rev3-dependent TLS activity are emerging that involve the genes implicated in the chromosome instability syndrome Fanconi anemia (FA). Interestingly, like TLS-deficient cells, FA-deficient cells exhibit hypersensitivity to DNA cross-linking agents and are hypomutable (62, 87, 171, 187, 204, 215). More specifically, it has been reported that *Rev1* and *Rev3* are epistatic to *FANCC* with respect to survival after cisplatin exposure in DT40 cells and that Rev1 colocalizes with FANCD2 after the blockage of replication in HeLa cells (187). Another recent study shows that the FA core complex is required for mutagenesis and efficient Rev1 focus formation in mammalian cells in a manner that is independent of PCNA monoubiquitination (171). These results contribute to the expanding field of TLS regulatory mechanisms that are not necessarily related to PCNA modifications.

Rev1 has also been shown to have an unanticipated role in preventing trinucleotide repeat expansion, particularly for those with hairpin-forming capacity. This as-yet poorly understood role of Rev1 may be relevant to neurodegenerative diseases (38, 43). Furthermore, Rev1, as well as Rev3 and Rev7, participates in nuclear mutagenesis induced by mitochondrial dysfunction, localizes to the mitochondria, and contributes to mitochondrial mutagenesis in *S. cerevisiae* (220, 274). Given the connection of mitochondrial function to disease, these functions of TLS polymerases may be associated with human diseases.

Pol ζ (Rev3/Rev7)

DNA Pol ζ is a heterodimer composed of the Rev3 catalytic subunit and the Rev7 accessory subunit (185). *REV3* was identified in the same screen for reversionless mutants in *S. cerevisiae* as *REV1* (137). *REV7* was isolated by a similar strategy a few years later (125). Like *rev1* mutants, *rev3* and *rev7* mutants are severely defective for spontaneous mutagenesis, as well as for mutagenesis induced by a wide variety of DNA-damaging agents, and for mutations induced in various DNA repair and tolerance pathway mutant backgrounds (123). *REV1*, *REV3*, and *REV7* are considered to be in the same branch of the *RAD6* epistasis group based on phenotypic similarity and limited epistasis analysis (88, 123). Like *REV1*, DNA Pol ζ plays a key role in most mutagenesis from yeast to humans (34, 64, 137, 168) as well as in cisplatin resistance in human cancer cells (145). Together, Rev1 and DNA Pol ζ are thought to mediate the vast majority of the mutagenic class of DNA damage tolerance in vivo.

Pol ζ's catalytic activity. Unlike most of the TLS polymerases, which are Y family DNA polymerases, Rev3 is a member of the B family, which includes the highly accurate replicative DNA polymerases DNA Pols δ, ε, and α (123, 173). In contrast to most other B family replicative polymerases, DNA Pol ζ lacks the motifs characteristic of a 3′-to-5′ exonuclease activity (123). Although it can bypass certain lesions such as a *cis-syn* TT dimer and perform both the insertion and extension steps opposite a thymine glycol lesion in an error-free manner (103, 185), Pol ζ appears to be particularly specialized to extend distorted base pairs, such as mismatches that might result from inaccurate base insertion by a TLS polymerase or a base pair involving a bulky DNA lesion (123, 217). In combination with a relatively high error rate for base substitutions, this proficiency for extending mismatches is what allows Pol ζ to contribute significantly to mutagenesis (123, 278). The accessory subunit of Rev3, Rev7, significantly enhances the polymerase activity of Rev3 (185). Despite the lack of conserved PCNA interaction motifs, Pol ζ exhibits increased lesion bypass activity in the presence of PCNA (60). However, stimulation of Pol ζ activity is not observed with either mo-

noubiquitinated PCNA or the alternative 9-1-1 processivity clamp (59, 190).

Other Pol ζ functions and protein interactions. Although it is a very large protein, Rev3 does not contain any known protein-protein interaction modules or other regulatory motifs (Fig. 3). In *S. cerevisiae*, Rev3 interacts with the C-terminal 100 amino acids of Rev1 in vitro, and this interaction stimulates the ability of Pol ζ to extend mismatches and bypass specific lesions (4, 74). However, the majority of the regulation of Pol ζ activity appears to occur through the accessory factor of Rev7. Rev7 contains a HORMA (*Ho*p1/*R*ev7/*Ma*d2) domain known to interact with chromatin (9). Due to its homology with Mad2, Rev7 is also known as Mad2L2 and Mad2B in higher eukaryotes. In yeast, Rev7 binds to the 9-1-1 alternative DNA processivity clamp, which participates in DNA damage signaling and checkpoint, and this interaction may recruit DNA Pol ζ to sites of DNA damage (229). Additionally, Rev7 interacts with Rev1 (70, 176, 197, 240, 243), which seems likely to promote localization of DNA Pol ζ to DNA lesions.

The physical and genetic interactions of Rev1 with DNA Pol ζ are complex. Despite the fact that each of the three proteins interacts with the others (see above), a heterotrimer of Rev1, Rev3, and Rev7 does not appear to be formed between purified proteins, as binding of Rev1 to Rev7 inhibits interaction of purified Rev1 and Rev3 in vitro (4). These findings indicate that the architecture of the Rev1-Pol ζ complex is intricate and that several subcomplexes may exist, possibly in a regulated manner. It is also possible that the posttranslational modifications of Rev1 mentioned above may influence the nature of Rev1's interaction with DNA Pol ζ in vivo.

Although Rev1, Rev3, and Rev7 are generally believed to work together, the functions of Rev1 and Pol ζ are not entirely overlapping. For example, *REV1* appears to act independently of *REV3*/*7* in the generation of sister chromatid exchanges during the recombinational bypass mode of damage tolerance (200). Additionally, Rev1's role in preventing trinucleotide repeat expansion is independent of both its own catalytic activity and that of DNA Pol ζ. This suggests that for some cellular roles, Rev1 can also act alone (38). Moreover, *REV7* appears to have a distinct and independent function in cell cycle control (see below).

Loss of Pol ζ causes embryonic lethality in mice (18, 47, 248, 260), indicating that during rapid proliferation, mammalian cells require a function of Pol ζ. The inability to study *rev3* mutant cell lines in mammalian systems has hampered understanding of Pol ζ function. However, studies with the chicken DT40 line have provided insight into the role of Pol ζ in vivo, in particular, the contribution of *REV1*, *REV3*, and *REV7* to chromosomal rearrangements during recombination and interstrand cross-link repair (200, 231). In *S. cerevisiae*, an organism in which *rev3* mutants are viable, *REV3* has also been shown to participate in homologous recombination by mediating the mutagenesis observed in the break-induced replication subpathway of homologous recombination (90, 221).

Despite being a relatively small protein, Rev7 participates in many protein-protein interactions apart from its interactions with Rev1 and Rev3. Many of these additional Rev7 interactions are with cell cycle proteins, indicating a potential link between TLS and regulation of cell growth. In higher eukaryotes, Rev7 has been shown to interact with the specificity factors Cdh1 and/or Cdc20 of the anaphase-promoting complex/cyclosome (APC/C), as well as the spindle checkpoint protein Mad2, both key regulators of mitotic progression (32, 177, 211). Interaction with Rev7 inhibits the ubiquitin ligase activity of the APC/C and prevents the onset of mitotic anaphase (32, 211). Interestingly, Rev7 was recently shown to be the target of a bacterial effector protein during *Shigella* infection. Upon delivery of the bacterial IpaB protein into the cytoplasm, human epithelial cells arrest in G_2/M due to aberrant activation of the APC/C by the removal of the Rev7 inhibition (94). Therefore, Rev7 plays a key in vivo role in cell cycle regulation. Rev7 also interacts with a variety of other proteins involved in the cell cycle and regulation of cell growth: the HCCA2 transcriptional activator involved in cell cycle control (139), the Elk1 transcription factor affecting cell cycle progression and the DNA damage stress response (275), the PRCC cancer protein implicated in RNA splicing and mitotic progression (258), two metalloproteases involved in cell proliferation and signaling (186), and the adenovirus death protein (269).

Regulation of Pol ζ. Multiple mechanisms collaborate to keep Pol ζ levels low (123), indicating that overexpression may be detrimental to cells. Indeed, overexpression of Pol ζ causes increased UV-induced mutagenesis and decreased UV resistance in *S. cerevisiae* (219). Both yeast and human *REV3* transcripts contain small upstream open reading frames which presumably reduce the translational efficiency of the major open reading frame encoding the Rev3 protein (64, 65, 123, 142). Additionally, alternative splicing of the human *REV3* gene produces an in-frame stop codon in ~40% of *REV3* transcripts, further reducing the levels of Rev3 protein (123). *REV3* transcript levels are upregulated above the normally low basal levels in late meiosis in yeast (234). Reminiscent of the cell cycle regulation of Rev1 in *S. cerevisiae*, Rev3 chromatin association in human cells has a cell cycle-regulated pattern, showing highest levels during the G_1/S boundary, which decreased during S phase and increased again during late S and G_2 (25).

Mammalian cells possess additional mechanisms to regulate TLS activity that are not found in *S. cerevisiae*, such as those involving the p53 and p21 proteins, which are emerging as regulators of TLS. In human colon carcinoma cells, loss of p53 or DNA mismatch repair causes an increase in *REV3* and *REV1* mRNA levels (143). These backgrounds also exhibit increased rates of the development of cisplatin resistance likely caused by enhanced TLS-induced mutagenesis. In mammalian cells, p53 and p21 suppress TLS activity and, counterintuitively, stimulate UV-induced monoubiquitination of PCNA (12). Subsequent studies shed light on this contradiction, exposing the problem of p21 degrading after exposure to UV damage (110, 129, 130, 235). Using a nondegradable p21, Soria et al. reported the inhibition of PCNA ubiquitination in the presence of stabilized p21 (236).

Given its roles in mutagenic TLS and cell cycle control, it is not surprising that Rev3 and Rev7 have been studied with respect to cancer (139, 222). Rev7 overexpression has been found in colon cancer, and this correlates with chromosomal instability and patient mortality (222). Curiously, another study found that *rev3* transcript levels were downregulated in colon carcinomas (25). The contradictory data reveal the complexity of cancer and suggest that TLS polymerases could have roles in

cancer in specific contexts. Consequently, changes in the regulation of Rev7 and Rev3 levels in vivo may be connected to cellular events related to disease.

Pol κ (DinB)

In contrast to the *REV* genes, Pol κ was not identified by its involvement in mutagenesis or its resistance to DNA-damaging agents. Rather, Pol κ was identified by homology searches for eukaryotic orthologs of the *E. coli dinB* gene (101). Although *dinB* was first discovered in 1980 as a gene that was significantly upregulated during the bacterial SOS response (112), it was not until nearly 20 years later that its polymerase activity was demonstrated (251). Found in all domains of life (199), DinB/Pol IV (as it is known in *E. coli*) and Pol κ (as it is known in eukaryotes) is the most highly represented and most strongly conserved of all the TLS polymerases. The pervasiveness of Pol κ argues that this protein contributes to the normal functioning of all cells. It has been surprising, then, that loss of Pol κ generally reveals only mild phenotypes (see below). Although the bacterial ortholog, DinB, has been studied extensively (for a review, see reference 98), eukaryotic Pol κ has been less characterized, particularly in terms of its role(s) in TLS in vivo. This discrepancy derives in part from the fact that Pol κ is conspicuously absent from what is arguably the best-studied single-cell eukaryote, *S. cerevisiae*. Pol κ orthologs have been identified in other related fungal species, though, including the fission yeast *Schizosaccharomyces pombe*. Organisms that lack a DinB homolog may possess another protein that plays a functionally redundant role.

Pol κ's catalytic activity. With regard to in vitro DNA replication on undamaged DNA, mammalian Pol κ is relatively accurate compared to other TLS polymerases; human Pol κ has a misinsertion frequency of 1 in every 10^2 to 10^3 nucleotides replicated (116). Although the bacterial and archaeal orthologs of DinB demonstrate a marked proclivity for −1 frameshifts in vitro and when overproduced in vivo (67, 113, 116, 216), mammalian Pol κ appears to be more restricted in this activity both in vitro and in vivo (196). With respect to DNA damage bypass, Pol κ has limited ability to synthesize across numerous DNA lesions (for reviews, see references 16 and 268); however, it can bypass many N^2-adducted dG residues, including N^2-dG-linked DNA-peptide cross-links, both efficiently and accurately (see, e.g., references 10, 97, 170, and 271). Indeed, it appears that Pol κ is specialized in its ability to bypass N^2-adducted dG lesions; Pol κ operates with high accuracy and strikingly increased catalytic efficiency opposite N^2-furfuryl-dG and N^2-(1-carboxyethyl)-2-dG residues relative to an undamaged dG (97, 271). Significantly, like Pol ζ, Pol κ appears to be specialized to extend mismatched primer termini and thus seems likely to function as a second "extender" polymerase when two TLS polymerases are required in concert to bypass a lesion (30, 150, 217). Furthermore, in vitro, the DNA synthesis activity of human Pol κ is stimulated in the presence of PCNA, replication factor C, and replication protein A but not by a single complex in the absence of the others (81).

Role of Pol κ in mutagenesis. The role(s) of Pol κ in mutagenesis is enigmatic. In contrast to deletion of Rev1 and Pol ζ, deletion of Pol κ does not appear to have a profound effect on either spontaneous or damage-induced mutagenesis. In mammalian cells, loss of Pol κ sensitizes cells to the killing by benzo[*a*]pyrene and moderately increases mutagenesis induced by this agent, suggesting that Pol κ bypasses N^2-benzo[*a*]pyrene dG adducts relatively accurately in vivo (10, 195). Loss of Pol κ is also associated with sensitivity to DNA-alkylating agents and to UV irradiation (193, 239), although sensitivity to UV in the absence of Pol κ seems likely to reflect its yet-to-be-defined role in nucleotide excision repair (193). Ectopic overexpression of human Pol κ in mammalian cell lines inhibits replication fork progression (212) and leads to general genomic instability, including increased DNA strand breaks, loss of heterozygosity, and aneuploidy (17).

Pol κ's protein interactions. Multiple protein-protein interactions likely regulate Pol κ function. Eukaryotic Pol κ interacts with the PCNA processivity clamp (human [81]), ubiquitin (mouse [72]), the 9-1-1 checkpoint clamp (*S. pombe* [104]), and Rev1 (mouse [70]). Many, if not all, of these interactions are important for Pol κ's function in vivo. For example, as noted below, mutations of Pol κ that disrupt its interaction with ubiquitin or with PCNA result in aberrant nuclear localization after DNA damage (72, 191). Additionally, the 9-1-1 complex, which is involved in signaling the DNA damage checkpoint via the clamp loader, localizes Pol κ to chromatin in replication-compromised *S. pombe* strains (104). Also, a mutant of the 9-1-1 clamp that perturbs DNA binding by Pol κ displays a reduction in point mutations.

Regulation of Pol κ. Pol κ relocalizes from a diffuse nuclear pattern into foci upon DNA damage (19, 20, 191). Focus formation by Pol κ requires both its PCNA interaction motif and its UBMs (72, 191) (Fig. 3). Interestingly, Pol κ relocalizes in response to DNA damage differently from the other Y family members, forming fewer spontaneous and damage-induced foci (20, 191). The reports disagree, however, on whether DNA Pol κ forms foci during S phase (20, 191).

A key source of regulation of Pol κ may be at the level of transcription. Murine Pol κ transcript levels increase after treatment with 3-methyl methylcholanthrene, a polycyclic aromatic hydrocarbon similar to benzo[*a*]pyrene (194). Notably, a change in Pol κ's transcript levels may be connected to cancer development in some contexts, as Pol κ transcripts are downregulated in some human colorectal tumors (136). Conversely, Pol κ transcripts are upregulated in non-small-cell lung cancers (202a). This increase in Pol κ transcripts correlates with the increased loss of heterozygosity in these tumors (17).

Pol η (Rad30A/XP-V)

Like Pol κ, the *rad30* gene was identified not on the basis of its contribution to mutagenesis but rather by its homology to the genes encoding the Rev1, UmuC, and DinB proteins. Its name reflects the slight sensitization of a *rad30* mutant in *S. cerevisiae* to UV irradiation (165). Indeed, under most circumstances, *rad30* mutants display very limited reduction in mutagenesis in yeast.

The Rad30/Pol η subfamily is found only in eukaryotes, where it is broadly conserved. Pol η is perhaps the most thoroughly characterized TLS polymerase, since in humans, loss of Pol η activity results in a cancer-prone syndrome known as xeroderma pigmentosum variant (XPV), which is characterized by an increased incidence of skin cancers and sensitivity to

sunlight (111, 132, 135, 157). Clinically, XPV is very similar to other forms of xeroderma pigmentosum, which result from mutations in any of six key nucleotide excision repair genes, but XPV cells are not defective in nucleotide excision repair (140, 223). This phenotype highlights the predominantly nonmutagenic role of Pol η, setting it apart from the more mutagenic functions of Pol ζ and Rev1.

Pol η's catalytic activity and role in mutagenesis. The phenotypes of mutants with DNA Pol η deficiencies and the in vitro activity of Pol η indicate that its major role is the nonmutagenic bypass of UV-induced DNA lesions. In particular, Pol η is the primary TLS polymerase responsible in many organisms for error-free bypass of *cis-syn* cyclobutane pyrimidine dimers (CPDs), one of the major lesions resulting from UV radiation (1, 63, 263). In vitro, Pol η has been shown to bypass CPDs with high accuracy and efficiency (100), and in vivo, it is thought to be responsible for restarting stalled replication forks and allowing continuous DNA synthesis past sites of UV damage (132). In the absence of Pol η, double-strand DNA breaks develop after UV radiation when unrepaired lesions are encountered during DNA replication, which can ultimately cause cell death or genomic rearrangements (61, 141). Furthermore, Pol η-independent CPD bypass, which is thought to involve other TLS polymerases such as Pol ζ and/or Pol ι, is significantly more mutagenic, presumably accounting for the increased frequency of cancer in XPV patients (126, 132, 157, 252). In addition to the severely distorting CPDs, in vitro, Pol η is also able to bypass a broad range of other DNA lesions, such as 7,8-dihydro-8-oxoguanine (84), (+)-*trans-anti*-benzo[*a*]pyrene-N^2-dG (277), acetylaminofluorene-adducted guanine (272), O^6-methylguanine (79), thymine glycol (120), and adducts derived from cisplatin and oxaliplatin (247). Aside from CPDs, purified Pol η is able to bypass other large and distorting lesions such as the cisplatin-induced 1,2-d(GpG) adduct (Pt-GG) and evidence exists for the importance of Pol η after cisplatin exposure in XPV cells (5, 6, 33).

Interestingly, though Pol η plays a major role in accurately bypassing particular types of DNA lesions, such as CPDs and 7,8-dihydro-8-oxoguanine, it exhibits among the lowest fidelity of any DNA polymerase on undamaged DNA in vitro (11, 42, 118, 127, 158, 217). In spite of its mutagenic potential, depletion of Pol η in human cells by small interfering RNA actually increases mutation frequency (36, 92), and *S. cerevisiae rad30* mutants do not display a major reduction in spontaneous or induced mutagenesis (165, 225). Similarly, Pol η knockout mouse embryonic fibroblasts show an increased UV-induced mutation frequency (28). Taken together, these results indicate that Pol η's normal function in vivo primarily reduces mutagenesis. Therefore, regulation of Pol η activity is thought to play a crucial role in modulating the mutagenic potential of Pol η in living cells.

Intriguingly, overexpression of Pol η in human cells does not increase mutagenesis and causes only a weak mutator effect in *S. cerevisiae* (114, 208), suggesting that Pol η is largely restricted from accessing undamaged DNA by additional regulatory mechanisms even when overexpressed. Pol η's potential for introducing mutations, though normally inhibited in somatic cells, is harnessed in a specific context. Pol η is the major mutator of A · T base pairs during the SHM step in antibody diversification in B lymphocytes (159, 209).

Pol η's protein-protein interactions. The regulation of Pol η's catalytic activity is directed in part through protein-protein interactions. Pol η interacts with the eukaryotic processivity clamp, PCNA, through its C-terminal PCNA-binding motif (PIP box) (Fig. 3) (108), and the interaction between PCNA and Pol η plays an important role in Pol η function. This is at least partially attributable to the stimulatory effect of PCNA on Pol η's TLS activity in vitro (76, 78, 105). Interestingly, the interaction between PCNA and Pol η is inhibited by p21, a protein discussed above with respect to regulation of TLS (236).

Although ubiquitinated PCNA is not required for Pol η to access stalled replication forks in vitro (189), Pol η's interaction with PCNA can be enhanced by the monoubiquitination of PCNA. Mammalian Pol η foci colocalize with foci of monoubiquitinated PCNA in the nucleus (108), and accumulation of Pol η foci in response to DNA damage is dependent upon monoubiquitinated PCNA (213), although a small proportion of cells (5 to 10%) do have Pol η foci in *rad18*$^{-/-}$ or *pol30*(*K164R*) mutants, in which PCNA is not monoubiquitinated (256). A similar proportion of cells contain Pol η foci in the absence of DNA damage, consistent with a model in which PCNA monoubiquitination induces Pol η's response to exogenous DNA damage, above a low level of uninduced DNA association by Pol η.

The dependence of Pol η's damage-induced foci on monoubiquitinated PCNA is attributed to Pol η's interactions with PCNA and ubiquitin (213), which appear to give Pol η a competitive advantage over the replicative Pol δ for PCNA association after DNA damage (256, 273). Pol η's interaction with monoubiquitinated PCNA is mediated by both the PCNA interaction motif (PIP box) and its ubiquitin-binding zinc finger (UBZ) domain (205) (Fig. 3). Mutants disrupting the UBZ, in either *S. cerevisiae* or mammalian Pol η, fail to complement the UV sensitivity of Pol η-deficient cells (21, 205), although at lower UV doses, Acharya et al. (3) have demonstrated partial complementation of the UV-sensitive phenotype of the *rad30*Δ strain. Monoubiquitinated PCNA may also promote TLS by enhancing Pol η's catalytic activity, but in vitro results have so far been inconsistent (59, 82).

Another protein which participates in the regulation of Pol η is Rad18, an E3 ubiquitin ligase that mediates PCNA monoubiquitination. Mouse Pol η has been found to have a direct physical interaction with Rad18, independent of the presence of DNA damage, via C-terminal regions of both proteins (256). Furthermore, in human cells, Pol η copurifies as a complex with Rad18, Rad6, and Rev1; the complex is enriched in the chromatin fraction in response to UV radiation or S-phase arrest (273), consistent with the model that Rad18 is involved in recruitment of Pol η to stalled replication forks. Pol η foci colocalize with Rad18 foci (256), and the formation and damage-dependent accumulation of Pol η foci are largely dependent on Rad18 (256).

Pol η may also be regulated by ubiquitination through a covalent attachment of a monoubiquitin moiety (21, 203, 205), although the functional significance of this modification is not yet understood. Ubiquitination of Pol η is dependent on the UBZ domain of Pol η. Intriguingly, the monoubiquitination of Pol η is not dependent on the postreplicative repair proteins

Rad6 and Rad18, nor is it responsive to DNA damage (205).

There is also a robust physical interaction between DNA Pol η and Rev1 in vertebrates and flies but only a weak interaction, if any, between Pol η and Rev1 in budding yeast (3, 70, 117, 243, 262). Thus, the functional interactions between TLS polymerases are complex and, to some extent, species dependent.

Regulation of Pol η. Transcriptional regulation of Pol η was demonstrated early. In *S. cerevisiae*, the *RAD30* transcript is induced three- to fourfold in response to UV radiation (165, 225). In mouse, however, expression of the XPV gene (encoding Pol η) is not induced by UV radiation; instead, it has been found to increase about fourfold during cell proliferation (264). The *RAD30* gene in *S. cerevisiae* has been placed in the *RAD6* epistasis group (165) but appears to function independently of both the error-free pathway defined by *RAD5* (165) and the error-prone TLS pathway which includes *REV1*, *REV3*, and *REV7* (165, 262).

Pol η forms foci spontaneously in a small percentage of untreated cells, suggesting that Pol η is localized to these sites to perform its lesion bypass activity. These foci accumulate in the majority of cells that have been treated with DNA-damaging agents such as UV or methyl methanesulfonate (105) and in cells subjected to hydroxyurea-induced replication stress (5, 20, 41, 105, 106). These foci are thought to form at sites of DNA damage since they colocalize with PCNA (5, 105, 106) and with Rad18 foci (256). Although it is assumed that the nuclear Pol η foci represent sites of TLS, focus formation does not necessarily imply activity. For example, a mutant form of Rad18 that is unable to form foci nonetheless activates DNA damage tolerance pathways (182). Recent data even reveal that Pol η is transiently immobilized in foci (228) supporting a model of TLS polymerases transiently probing the chromatin. Additionally, accumulation of Pol η foci is stimulated by the physical interaction of Pol η's UBZ domain with monoubiquitinated PCNA (21, 108, 213, 256). Together with the fact that Pol η mutants progress more slowly through S phase after DNA damage (5, 237), these findings have led to a model in which Pol η rescues replication forks that have stalled at sites of DNA damage by allowing continuous DNA synthesis past the lesion(s).

Pol ι (Rad30B)

Pol ι is most closely related to Pol η at the sequence level but is divergent enough to have distinct biochemical properties and function. In contrast to the wealth of information about Pol η, the role of Pol ι is less well understood. Pol ι is present not only in higher eukaryotes as initially thought (166, 199, 242) but in organisms scattered throughout the *Eukaryota*, including some yeasts (L. S. Waters, unpublished observation). Because Pol ι is lacking in *S. cerevisiae*, in which most genetic studies of TLS DNA polymerases have been performed, little is known about its genetic relationships to other DNA damage tolerance pathways.

The role of Pol ι is complex and not well understood; Pol ι is reported both to contribute to mutagenesis in some situations and not to be involved in mutagenesis in others (35, 45, 265). More recent data support that Pol ι is involved in UV-induced mutagenesis in Burkitt's lymphoma and XPV cell lines (69, 252). As for Pol η, however, mice and humans lacking Pol ι tend to develop cancer at an increased rate, suggesting that Pol ι in the presence of other DNA repair and tolerance pathways is not a major contributor to mutagenesis in vivo (35, 45, 128, 198, 265). Consistent with the lack of strong data indicating a mutagenic role in vivo, loss of Pol ι seems to have little consequence in SHM, as the 129/J strain of mice that possess a nonsense mutation in the Pol ι gene preventing its expression have normal immunoglobulin hypermutation (164). A recent report investigating the biological significance of Pol ι in human cells has demonstrated that cell lines depleted for Pol ι exhibit enhanced sensitivity to oxidative damage (210). Moreover, Pol ι interacts with the base excision repair factor XRCC1 and is recruited to sites of oxidative DNA damage in living cells, suggesting a role for Pol ι in the repair of DNA damaged by oxidative stress (210).

Pol ι's catalytic activity. Biochemically, Pol ι has been thought to be one of the least accurate DNA polymerases, especially opposite pyrimidines (163). Interestingly, though, Pol ι was recently shown to exhibit significantly different catalytic activities on both damaged and undamaged DNA when manganese was used as a cofactor rather than magnesium. Importantly, these altered catalytic properties with manganese included a dramatic increase in the ability of Pol ι to bypass a variety of DNA lesions (50). The structure of Pol ι uniquely allows for Hoogsteen base pairing which helps explain the varying catalytic efficiencies opposite different template nucleotides (178, 181). As with the polymerases discussed above, the catalytic activity of Pol ι is stimulated in the presence of PCNA, replication factor C, and replication protein A in vitro (75, 77, 250).

Regulation of Pol ι. Limited information exists for the regulation of Pol ι's protein expression or activity. Possible regulatory mechanisms can be inferred from gene expression and protein localization studies. For example, like for other TLS polymerases, *RAD30B* and mouse *Rad30b* mRNAs are highly expressed in the testis, with the mouse *Rad30b* expression occurring mostly in the postmeiotic round spermatids (166). Additionally, Pol ι interacts physically with Pol η, and this interaction is required for its localization into DNA damage-induced foci (106). Similar to the case for the other TLS polymerases, the PCNA interaction motif and UBMs of Pol ι (Fig. 3) are also required for localization into foci after DNA damage, indicating that recruitment to stalled replication forks by monoubiquitinated PCNA mediates the function of Pol ι (21, 250). However, it should be noted that the biological relevance of the interaction with monoubiquitinated PCNA has not yet been tested for Pol ι.

Other Non-Y Family DNA Polymerases Capable of TLS

It is worth noting that there are other nonreplicative DNA polymerases that have various abilities to bypass DNA lesions and that synthesize DNA with a range of fidelities (reviewed in reference 172). The members of the X family of DNA polymerases (DNA Pols β, λ, and μ in eukaryotes), in particular, can insert nucleotides opposite to certain lesions (22, 172). After the Y family, the X family polymerases display the next lowest replication fidelity of the six major DNA polymerase families (119). The X family polymerases are occasionally referred to as translesion polymerases and indeed can lay a claim to the name. One A family member, Pol θ, exhibits a reduced fidelity relative to the other A family members and has been

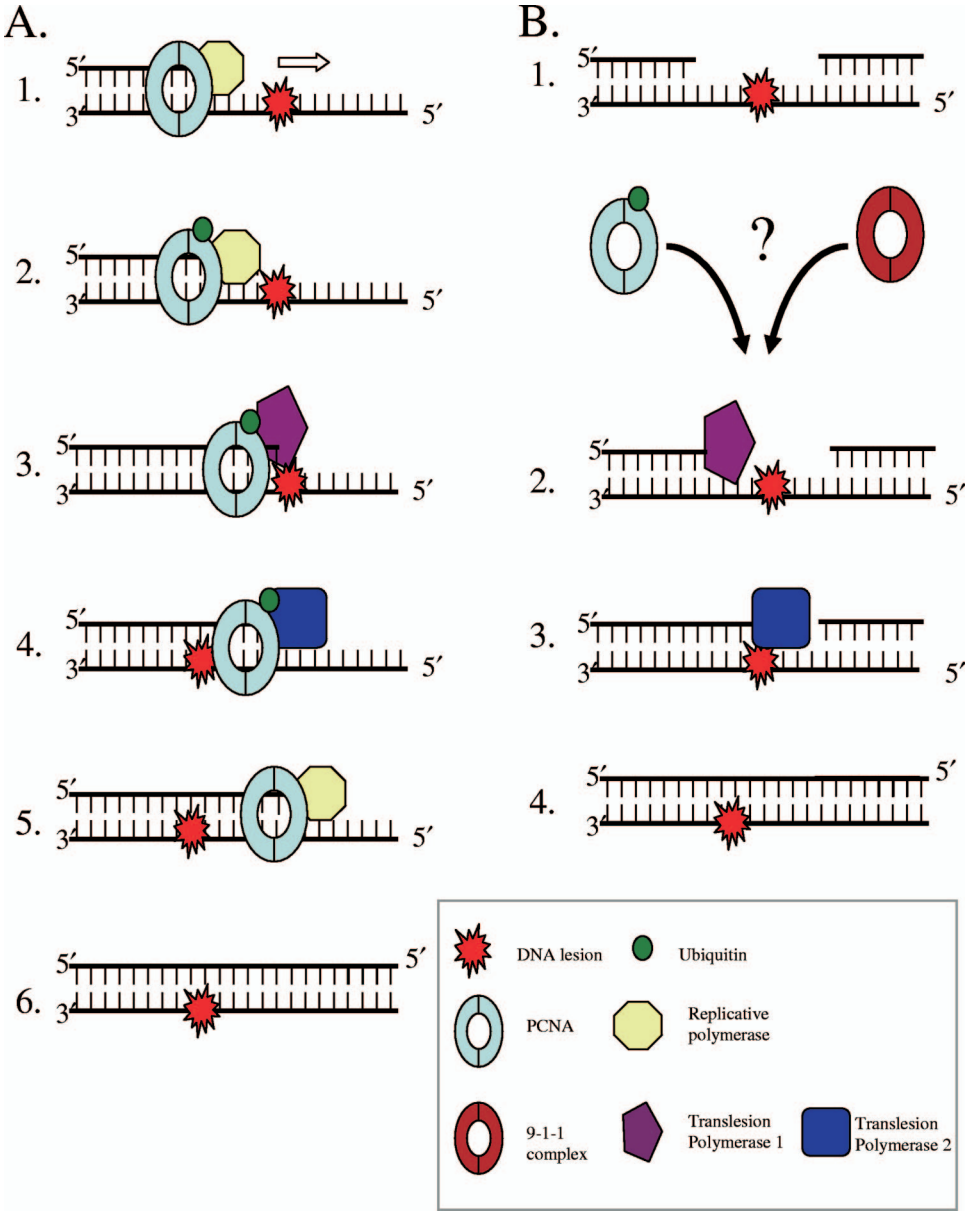

FIG. 4. Two nonexclusive models for TLS: the polymerase-switching model (A) and the gap-filling model (B). See text for details.

suggested to participate in TLS and SHM in vivo (8). Even the highly stringent replicative DNA polymerases have very weak abilities to replicate over certain lesions. In general, though, these non-Y family polymerases have other primary physiological functions, such as participation in base excision repair and nonhomologous end joining by the X family polymerases. Accordingly, the term TLS polymerases generally refers to the Y family and DNA Pol ζ, which clearly have specialized roles involved primarily in lesion bypass (53, 123).

GLOBAL MODELS FOR THE MECHANISM OF LESION BYPASS BY TLS POLYMERASES

The numerous genetic and biochemical data regarding the posttranslational regulatory strategies detailed above have been integrated into two models for DNA lesion bypass by TLS polymerases that are not mutually exclusive (Fig. 4): (i) the polymerase-switching model (51, 53, 133, 134, 161, 163, 214) and (ii) the gap-filling model (131, 133, 163, 257). There is compelling evidence for both models. It is likely that TLS polymerases act in a manner consistent with both models when spatially and temporally appropriate, dependent, for example, on the context of the DNA lesion or phase of the cell cycle.

Polymerase-Switching Model

In the polymerase-switching model (Fig. 4A), TLS polymerases act at the replication fork to enable replication to continue, bypassing DNA lesions that halt the forward progression of the replicative DNA polymerase. Access of TLS

polymerases to the DNA is governed by protein-protein interactions that mediate a polymerase handoff at the primer-template terminus from the replicative polymerase to one or more TLS DNA polymerases. A further switch restores the replicative DNA polymerase to the primer terminus, and accurate DNA synthesis resumes.

The polymerase-switching mechanism likely comes into play during times of active DNA replication. Upon DNA damage in eukaryotes, Rad18 is thought to bind to the ssDNA generated when a replication fork is blocked at a lesion, bringing the E2 ubiquitin ligase Rad6 with it to sites of DNA damage (13, 14). Once localized at or near the lesion, the Rad6/Rad18 heterodimer monoubiquitinates PCNA (89) (Fig. 4A, step 2). Many of the TLS polymerases have a basal affinity for unmodified PCNA in vitro through their PIP domains (76, 81, 83, 153, 250) or the BRCT domain, in the case of Rev1 (71). Thus, it is not entirely clear if the monoubiquitination of PCNA serves primarily to signal the need for TLS, simply serves to strengthen the interaction between PCNA and Y family TLS polymerases via their UBM or UBZ motifs, and/or facilitates a handoff between the replicative polymerase and the TLS polymerases (reviewed in reference 134) (Fig. 4A, step 3). The specific requirement for the UBM and UBZ domains of TLS polymerases for survival after DNA damage (89, 233) and for damage-induced relocalization of TLS polymerases into foci in vivo (see the references cited above and references therein), however, makes a tempting argument that the interaction between TLS polymerases and monoubiquitinated PCNA functions as a mechanism to stimulate a switch between a replicative polymerase and a TLS polymerase.

Once the TLS polymerase is recruited to the site of the lesion, an exchange is thought to occur between the replicative polymerase and the incoming TLS polymerase (Fig. 4A, step 3). The details of this process, however, are not well characterized. For example, it is unclear if the replicative polymerase must exit the primer terminus before the TLS polymerase can be recruited or if the replicative polymerase somehow aids in this transaction (as has been suggested for the Pol32 subunit of the replicative Pol δ [91, 169]). In addition, it has recently been demonstrated in vitro that *S. cerevisiae* Pol η cannot gain access to the primer terminus while it is occupied by a moving replicative polymerase, suggesting that the stalling of the replicative polymerase is required to allow entry of Pol η onto the DNA (280).

Following the handoff between the replicative and TLS polymerase on the primer terminus, the subsequent nucleotide insertion across and extension past the lesion may require the concerted action of two or more TLS polymerases (Fig. 4A, step 3 to 4). In eukaryotes, extension from a lesion is thought to be primarily mediated by Pol ζ, and also to some extent by DNA Pol κ, due to the distortion or mismatched base pair often produced by TLS (217, 218). Finally, once the TLS polymerase(s) is able to bypass the lesion and extend past the distorting mismatch, a further polymerase switch, perhaps facilitated by the deubiquitination of PCNA (92), reinstates the replicative DNA polymerase at the primer terminus. Accurate DNA synthesis can therefore resume and the replication fork again moves forward (Fig. 4A, step 5). Following bypass by TLS, the lesion would again be a substrate for removal by DNA repair mechanisms. The described mechanism likely has more layers of complexity in vivo given that monoubiquitinated PCNA persists for hours after the removal of UV damage in human cells (188).

While PCNA plays a significant role in TLS-assisted DNA lesion bypass, it is likely not the only factor involved in the recruitment and polymerase exchange reaction. For example, eukaryotes also contain an alternative processivity clamp, termed the 9-1-1 complex, which is loaded onto regions of ssDNA by an alternative clamp loader, and functions in the DNA damage checkpoint response (24). The 9-1-1 clamp physically interacts with the Rev7 subunit of DNA Pol ζ in *S. cerevisiae* (229) and with Pol κ in *S. pombe* (104). Loss of the alternative clamp and clamp loader lowers the mutation frequencies in both organisms (104, 207, 229), and loss of the alternative clamp loader prevents Pol κ from being recruited to chromatin in *S. pombe* (104). Additionally, in a striking report, Fu et al. have recently shown that the Rad6/Rad18 heterodimer monoubiquitinates the Rad17 subunit of the 9-1-1 complex to induce the DNA damage response in *S. cerevisiae* (54). Thus, the interplay of the two eukaryotic clamps in the recruitment of TLS polymerases and other factors is just beginning to be elucidated. Finally, a clamp may not be required in every circumstance of lesion bypass because, as noted above, Rev1 may interact with the DNA on its own by utilizing its BRCT domain (88) and, via its last 100 amino acids, may target other TLS polymerases to the site of the DNA lesion (44a, 70, 176, 197, 243).

Gap-Filling Model

The second model, gap filling (Fig. 4B), has been proposed to account for TLS-assisted DNA lesion bypass outside the context of the replication fork, when DNA damage may reside in single-stranded gaps. In this situation, the purpose of TLS is not to restart a stalled replication fork but rather to seal gaps that have resulted from the replication machinery repriming downstream of the blocking lesion, thereby leaving behind a ssDNA gap opposite the lesion. Repriming events leading to single-stranded gaps were first suggested to arise in *E. coli* by Rupp and Howard-Flanders (226) and more recently suggested to arise in *S. cerevisiae* by Lopes et al. (151), either by initiating a new Okazaki fragment on the lagging strand or by repriming on the leading strand (86). Alternatively, gaps containing lesions can be formed as a result of processing of closely spaced lesions on opposite DNA strands or by the processing of interstrand cross-links. It would be expected that this gap-filling mechanism would be utilized primarily outside of S phase, during G_1 or G_2/M phases of the cell cycle. It could, however, also occur during the later stages of S phase.

In the gap-filling model, once the cell identifies a need for lesion bypass, the TLS polymerase(s) is presumably directed to the ssDNA gap. This localization may involve many of the same factors used in polymerase switching, including PCNA, the 9-1-1 alternative clamp, and Rev1, which in *S. cerevisiae* is upregulated after the bulk of replication is complete during late S/G_2/M (227, 257). In this situation, handoffs with the replicative polymerase are not expected to contribute significantly in the recruitment of the TLS polymerase(s) but might come into play after the lesion is bypassed if the remaining gap after the lesion is large. Indeed, in *S. cerevisiae*, ssDNA gaps of

hundreds of nucleotides have been observed after UV irradiation (151). Following DNA lesion bypass and subsequent resealing of the nick with DNA ligase, the lesion would now be a substrate for removal by DNA repair pathways and could be removed before the next round of replication.

Choosing the TLS Polymerase for Lesion Bypass

One of the most perplexing questions regarding TLS-assisted lesion bypass is how the "correct" TLS polymerase is selected to bypass a particular DNA lesion out of the pool of multiple possible TLS enzymes in vivo. It has been suggested that transient association of several polymerases with the DNA lesion at the primer terminus may occur sequentially until the best-suited polymerase is able to perform lesion bypass (163). In such models, specificity of TLS for bypass of a particular lesion is imparted by a passive trial-and-error approach based on the inherent efficiency of TLS polymerases opposite their cognate lesion. However, the many levels of regulatory controls and protein-protein interactions discussed in this review likely constrain which DNA polymerases are able to access a given primer terminus in a particular biological context. Examples include local increases in polymerase concentration by DNA damage induction (as in the case of Pol κ [194]) or by cell cycle regulation (as in the case of Rev1 [227, 257]), the ubiquitination state of PCNA, the interaction of TLS polymerases with monoubiquitin through UBMs, the ubiquitination/deubiquitination of TLS polymerases themselves, undiscovered modifications of these proteins, or the interaction of Rev1 with the other TLS polymerases. Ultimately, for both models of TLS lesion bypass, the differential primer/template affinities, processivities, and bypass activities of translesion polymerases may be the primary mechanism by which a particular DNA polymerase gains access to the DNA (56, 93, 121, 162).

RELATIONSHIP BETWEEN TLS POLYMERASES AND CANCER

Although they may have high accuracy opposite certain lesions, the fact that TLS polymerases have poor fidelity on undamaged DNA suggests that they are tightly regulated in vivo to avoid rampant mutagenesis. As detailed above, when overexpressed or inappropriately regulated, certain TLS polymerases confer a hypermutator phenotype (16, 19, 67, 113, 192) and/or change replication fork progression (15, 56, 93, 138, 212). Why, then, has there not been a stronger correlation between improper regulation of TLS and cancer? Perhaps the multiple overlapping systems for regulation of TLS provide the answer. For example, in the case of TLS polymerase overexpression, it may be the relative availability of accessory proteins used to direct TLS polymerases to the sites of DNA lesions that prevents rampant mutagenesis. In contrast, loss of TLS polymerases may have a greater effect upon multicellular organisms than overexpression. Indeed, loss of Pol η results in the variant form of XPV, a condition which renders one highly sensitive to the effects of UV light and susceptible to cancer (111, 132, 135, 157). Additionally, loss of Pol ζ leads to early embryonic lethality in mice (18, 47, 248, 260). While mouse models have not detected profound phenotypes upon single deletions of the TLS Pols κ and ι, there may be considerable redundancy between the roles of TLS polymerases in multicellular organisms that mask the effects of the loss of a single TLS polymerase. More profound phenotypes may be detected only upon the simultaneous loss of multiple TLS polymerases.

EVOLUTIONARY SIGNIFICANCE OF TLS POLYMERASES

Why are TLS polymerases that can actively cause mutagenesis so conserved throughout all domains of life? The risk to the cell of potential mutations and replication perturbation is presumably outweighed by the fact that TLS polymerases confer a measure of resistance to DNA-damaging agents. In general, the type of mutations created by TLS, i.e., base pair substitutions, are less detrimental to the integrity of the genome than translocations and other gross chromosomal rearrangements that can occur in the absence of TLS.

Evidence exists to show that the use of TLS polymerases is not trivial. In mammals, TLS polymerases contribute significantly to lesion bypass, as it has been estimated that ~50% of DNA damage tolerance events occur through TLS rather than the more error-free recombinational bypass pathways (10). Furthermore, the striking phenotypes associated with XPV dramatically underscore the significance of TLS to human health. Some modest phenotypes observed for TLS-deficient cells may be a result of overlapping functionality. For example, under certain conditions error-free tolerance may compensate for the loss of TLS, masking the true involvement of TLS polymerases in DNA damage resistance in cells. In addition, TLS polymerases may provide important functions to cells by aiding in replication of undamaged but difficult DNA substrates, such as the recently observed contribution of Rev1 to trinucleotide repeat stability (38), D-loop extension during homologous recombination by Pol η (111, 167), or other, as-yet-unknown structures.

Since the majority of mutations are deleterious, most organisms have evolved mechanisms that keep their mutation rates extremely low (44), and the complex control of TLS DNA polymerases discussed in this review help achieve that end. Nevertheless, an increase in the genetic variation within a population can be beneficial under adverse conditions, as it increases the chance of emergence of a variant that is better able to withstand the stress (49, 57). Thus, the mutations introduced by TLS polymerases can be an important factor in evolution by increasing the genetic variability in response to stresses that damage DNA. In bacteria, TLS polymerases have been implicated in adaptive mutagenesis—the ability to induce mutations upon cellular stress (49, 57). Additionally, in higher eukaryotes, the mutagenic capacity of TLS polymerases has been harnessed for SHM, the generation of mutations in the variable regions of antibodies produced by B-cell lymphocytes (31). Thus, despite potentially deleterious mutagenic effects, TLS polymerases presumably provide more benefits than disadvantages to cells, consistent with the observation that TLS polymerases have been found in all organisms whose genomes have been sequenced to date.

CONCLUDING REMARKS

Cells have developed specialized translesion polymerases to complete replication in the face of DNA damage, either at stalled replication forks or at sites of gaps containing lesions. The use of TLS polymerases to bypass DNA lesions provides resistance to DNA-damaging agents, the ability to restart stalled replication forks or fill in ssDNA gaps found in the genome after DNA damage. However, this comes at the potential cost of increased mutation frequencies. To counteract the mutagenic risk of using TLS polymerases, cells have developed elaborate regulation strategies. The regulation mechanisms detailed here are likely to increase in complexity as our knowledge in this field grows. The past decade has seen a profound increase in our knowledge of TLS polymerases, and the future promises to reveal further insights into the mechanism of action of these intriguing enzymes.

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