Damage repair DNA polymerases Y

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The newly found Y-family DNA polymerases are characterized by low fidelity replication using an undamaged template and the ability to carry out translesion DNA synthesis. The crystal structures of three Y-family polymerases, alone or complexed with DNA and nucleotide substrate, reveal a conventional right-hand-like catalytic core consisting of finger, thumb and palm domains. The finger and thumb domains are unusually small resulting in an open and spacious active site, which can accommodate mismatched base pairs as well as various DNA lesions. Although devoid of a 3′ → 5′ exonuclease activity, the Y-family polymerases possess a unique 'little finger' domain that facilitates DNA association, catalytic efficiency and interactions with auxiliary factors. Expression of Y-family polymerases is often induced by DNA damage, and their recruitment to the replication fork is mediated by β-clamp, clamp loader, single-strand-DNA-binding protein and RecA in *Escherichia coli*, and by ubiquitin-modified proliferating cell nuclear antigen in yeast.

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Abbreviations

PDB	Protein Data Bank
PCNA	proliferating cell nuclear antigen
SSB	single-strand-DNA-binding protein
SUMO	small ubiquitin-related modifier
TLS	translesion synthesis
UV	ultraviolet

Introduction

It was discovered thirty years ago that ultraviolet (UV) light, which causes covalent linkage between adjacent pyrimidines in DNA, induces expression of over 40 proteins in *Escherichia coli*, a so-called SOS response that enables cells to survive UV damage at the cost of an increased mutation rate [1]. Two of the UV-induced mutagenic proteins, UmuC and UmuD′ enable DNA replication to bypass covalently linked *cys–sin* T–T photodimers and 6–4 T–T or T–C photoproducts, which would otherwise stall the DNA replication fork. At the same time, however, UmuC and UmuD′ cause a large number of mutations by reducing the accuracy of DNA replication [2,3]. Owing to the difficulty of producing soluble and functional UmuC and a lack of sequence similarity to proteins of known function, UmuC and UmuD′ were long thought to modify or 'blindfold' *E. coli* DNA Pol III, which normally replicates DNA, and enable it to carry out mutagenic but translesion synthesis (TLS). In the late 1990s, production of soluble UmuC and reconstitution of the UmuD′(2)C complex led to the surprising result that UmuD′(2)C actually synthesizes DNA instead of modifying DNA polymerase [4,5]! UmuD′(2)C has therefore been rechristened Pol V after DNA polymerase Pol I, II, III and IV (DinB) of *E. coli*.

With the rapid expansion of genomic databases, over 100 homologues of UmuC have been identified in bacteria, archaea and eukarya forming a new family of DNA polymerases, named the Y-family after the existing A, B, C and X families of DNA polymerases [6•]. The prototypical Y-family polymerases include DinB (damage induced) and UmuC, which are also known as Pol IV and Pol V in *E. coli*, respectively, and the eukaryotic Rev1 and RAD30, which have been renamed Pol ζ and Pol η according to the alphabetic convention [7–10]. The Y-family polymerases are of variable size, ranging from 350 to 800 amino acid residues, but share five conserved sequence motifs distributed among the N-terminal ~250 amino acid residues [11]. Interestingly, different Y-family members exhibit different lesion bypass abilities and different mutation spectra. For example, Pol IV and Pol κ (eukaryotic DinB homologue) are able to bypass abasic and bulky DNA adduct lesions and make both base-substitution and frameshift mutations [12,13,14•,15]; Pol η is specialized to faithfully synthesize AA opposite a TT dimer [16], and Pol ι prefers to insert G instead of A opposite T [17,18]. Human Pol η was first identified as the XP-V protein, encoded by the xeroderma pigmentosis variant gene, which reflects the relationship between DNA repair and cancer biology [8,19].

There are three main questions regarding the Y-family polymerases: first, whether they are structurally related to other DNA polymerases; second, what allows these polymerases to synthesize DNA with low fidelity yet faithfully bypass replication-blocking lesions; and third, how cells manage to coordinate the activities of multiple different polymerases at a replication fork. In a short span of four months in 2001, four groups independently reported the crystal structures of three Y-family polymerases. This review summarizes the main structural

Table 1

DNA polymerases*.

Family	Examples	Error rate	Function
A	Pol I, T7, Taq	10^{-5} to 10^{-6}	Replication
B	Pol II, RB69, PolB, Pol α, δ, ε	10^{-5} to 10^{-6}	Replication
C	Pol III α subunit	10^{-5} to 10^{-6}	Replication
D	PolD	10^{-5} to 10^{-6}?	Replication?
X	Pol β, λ, μ, σ, TdT	10^{-4} to 10^{-5}	Repair, Ig, TCR
Y	DinB, UmuCD′, Dpo4, Dbh, Pol ζ, η, ι, κ	10^{-2} to 10^{-4}	Mutagenic, TLS

* Representative members of each DNA polymerase family are color coded black for bacterial (Pol I, II and III from *E. coli*), red for eukaryotic and green for archaeal. Most eukaryotic replicative DNA polymerases belong to the B family. Pol γ is mitochondrial and can be placed in either A or B family. The error rate of PolD is yet to be determined and its role in replication to be confirmed. Ig, immunoglobulin; TCR, T-cell receptor.

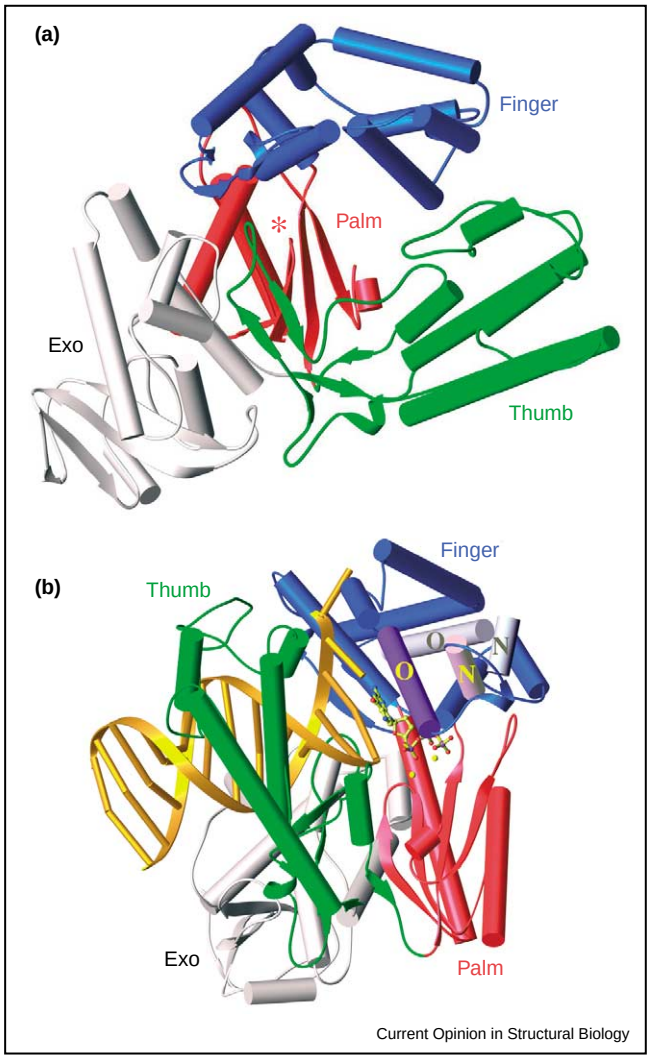
features of the Y-family polymerases, possible mechanisms for lesion bypass and low fidelity synthesis, and the correlation between DNA damage and recruitment of the Y-family polymerases to a replication fork.

DNA polymerases

On the basis of sequence similarity, DNA polymerases involved in DNA replication during the regular cell cycle are divided into the A, B, and C families, represented by *E. coli* DNA polymerases I, II and III (Table 1). The A, B and C family polymerases possess a catalytic core, which performs highly accurate and processive DNA replication, and a 3′ → 5′ exonuclease activity, which performs a proofreading function that further improves fidelity. Recently, a distinctive yet related replicative polymerase family was found in Archaea and called DNA Pol D (Table 1) [20]. Crystal structures of the A and B family members reveal a common right-hand-like architecture consisting of finger, thumb and palm domains and an active site in the palm domain composed of three conserved carboxylates and two metal ions (Figure 1a) [21–26]. Structural comparison of the polymerase alone and with DNA and nucleotide substrates reveals an induced-fit movement of the finger domain upon binding of a correct incoming nucleotide before catalysis (Figure 1b) [25].

The X family DNA polymerases, represented by DNA Pol β, are involved in DNA gap repair synthesis (e.g. during base excision repair). The enzymes have recognizable sequence motifs of a DNA polymerase but lack a 3′ → 5′ exonuclease domain and thus have no proofreading function. Crystal structures of Pol β in various stages of the catalytic cycle have been determined [27] and reveal a conventional polymerase architecture with a base recognition and fidelity check mechanism reminiscent of the A and B family DNA polymerases (see the recent review [28•]). The relatively small human Pol β (344 residues) contains a DNA lyase domain at its N-terminus,

Figure 1



Structure of Taq DNA polymerase (A family). **(a)** The catalytic core consists of palm (red), finger (blue) and thumb (green) domains. The asterisk marks the active site in the palm domain. The Exo domain (gray) contains the 3′ → 5′ exonuclease activity, but it is inactivated as a result of mutations in the Taq polymerase. **(b)** Taq Pol I complexed with DNA (gold) and an incoming nucleotide (ball-and-stick representation) perfectly base paired with the template. Helices O (purple) and N (pink) of the finger domain are in the 'closed' active conformation instead of the 'open' conformation (shown in gray) in the absence of a correct incoming nucleotide. This figure was made using the PDB coordinates of 1QSS (closed) and 2KTO (open). Figures 1–4 were made with RIBBONS [51].

which enables Pol β to bind gapped DNA substrates [29]. Pol λ, Pol μ and Pol σ are members of the X family identified in recent years and are likely to be involved in DNA repair and special DNA synthesis for cell development [30–33].

The A, B, C and X family DNA polymerases share one common feature: they are stalled by DNA lesions, such as

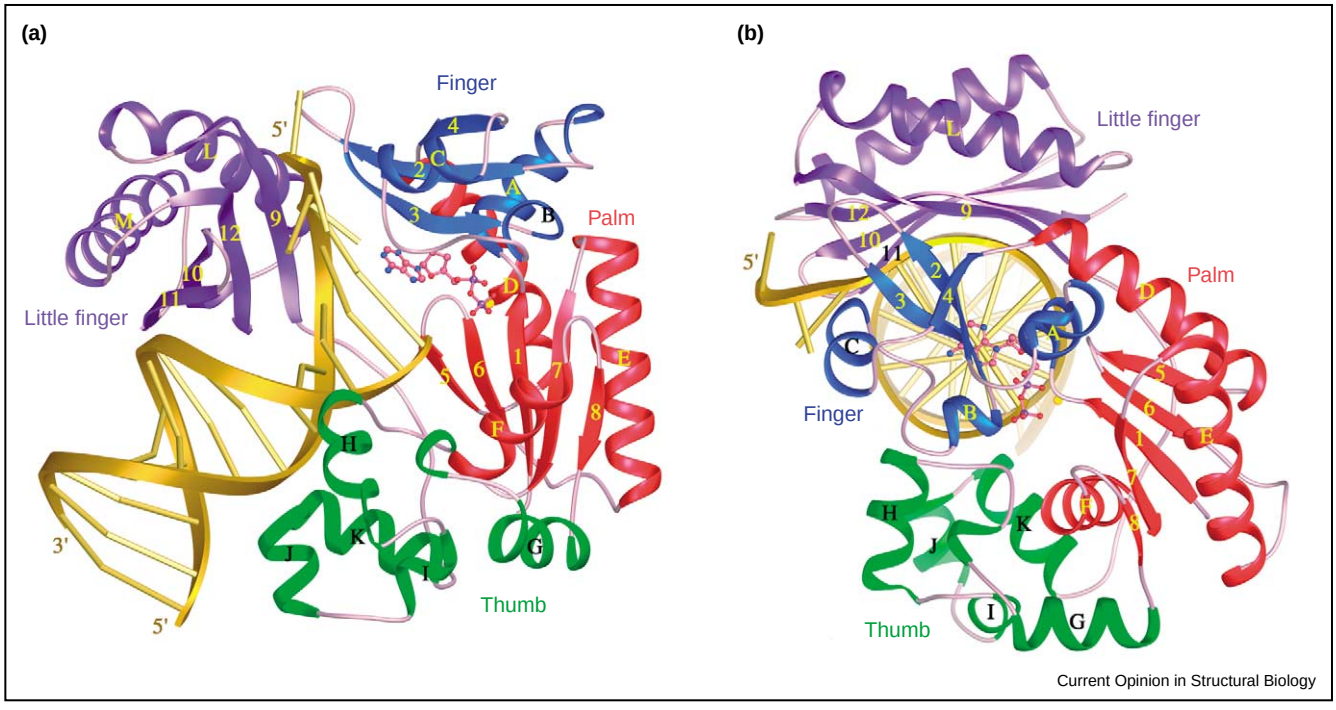
the photoproduct cyclobutane pyrimidine dimers (CPD), polycyclic aromatic DNA adducts, and abasic sites. Only the Y-family polymerases, which share no detectable sequence similarity with the A, B, C and X family polymerases, are able to efficiently perform translesion DNA synthesis [34••]. The Y-family polymerases are also implicated in somatic hypermutation of immunoglobulin genes [35•,36].

Structural features of the Y-family polymerases and functional consequences

The crystal structures of three Y-family polymerases, Dbh, Dpo4, both of which are archaeal DinB homologs, and *Saccharomyces cerevisiae* Pol η, unveiled a catalytic core consisting of palm, finger and thumb domains similar to all DNA polymerases and a unique C-terminal domain (Figures 2 and 3) [37•–39•,40••]. Three catalytically essential carboxylates, Asp-7, Asp-105 and Glu-106 in Dpo4, are located in the palm domain. These three carboxylates are conserved in the Y-family polymerases and coordinate two metal ions for the nucleotidyl-transfer reaction, as do the three carboxylates found in the active sites of the A, B, C and X family polymerases. The additional C-terminal domain of the Y-family polymerases has been called the 'little finger' in accordance with the nomenclature of palm, finger and thumb domains that is used in analogy to a right hand and because of its role in holding a DNA substrate opposite the thumb (Figure 2) [40••]. This C-terminal domain is also known as the 'wrist' in Dbh or the polymerase associated domain (PAD) in Pol η. After the little finger domain, Pol η contains an additional ~100 residues, which are not present in the crystal structure. Although the polymerase catalytic activity resides in the conserved N-terminal catalytic core, the C-terminal region is essential for TLS *in vivo*, perhaps for interacting with other cofactors regulating DNA synthesis [41,42•].

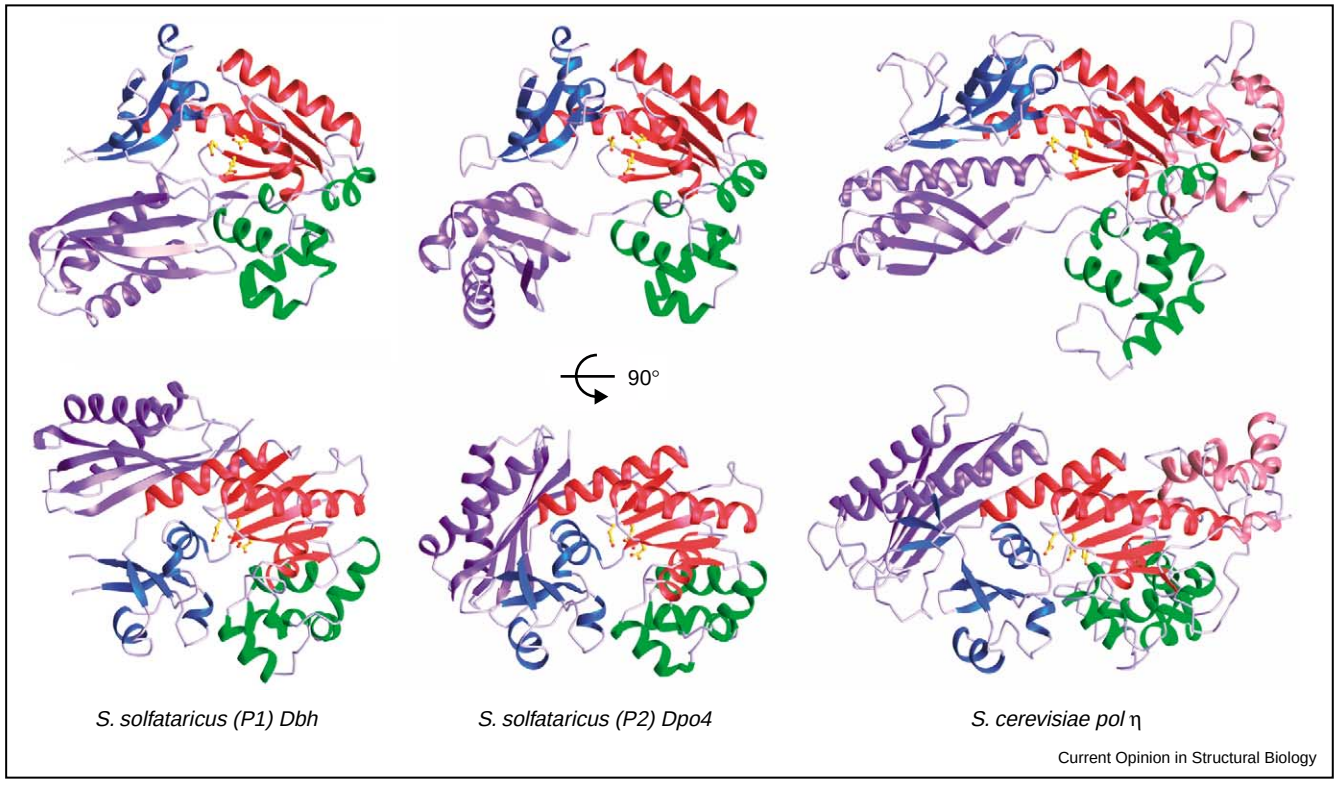
The thumb and finger domains of the Y-family polymerases are unusually small compared with the replicative polymerases and result in the DNA substrate being relatively solvent-exposed near the active site. The A and B family polymerases achieve high fidelity synthesis through intimate protein and DNA contacts so that only Watson–Crick base pairs with a smooth minor groove (Figure 4a) are accommodated at the active site and in the immediately upstream DNA duplex [21,23,24,26]. Dpo4, however, appears to make only a few van der Waals contacts with the replicating base pair at the active site, and no contact with any bases once they have passed through the active site (Figure 4b) [40••]. This polymerase appears to have little trouble accommodating a wobble base pair with protrusions into the minor groove at or beyond the active site. The spaciousness of the active site

Figure 2



Crystal structure of *Sulfolobus solfataricus* Dpo4 complexed with DNA and an incoming nucleotide (PDB code 1JX4). **(a,b)** Two views of the ternary complex in ribbon diagram. The palm domain is shown in red, finger domain in blue, thumb domain in green, and little finger domain in purple. DNA is in gold, incoming nucleotide (ball-and-stick) in pink and the metal ion in yellow. In (a) DNA is in the plane of the page and in (b) DNA is viewed down its helical axis.

Figure 3



Comparison of the three Y-family polymerases Dbh (PDB code 1K1Q), Dpo4 (PDB code 1JX4) and Pol η (PDB code 1JIH). The protein domains are shown in ribbon diagrams with the same color scheme as in Figure 2. The DNA complexed with Dpo4 is removed for clarity. Each structure is shown in two orthogonal orientations. The orientation of little finger domain (purple) relative to the catalytic domain apparently differs in Dbh versus Dpo4.

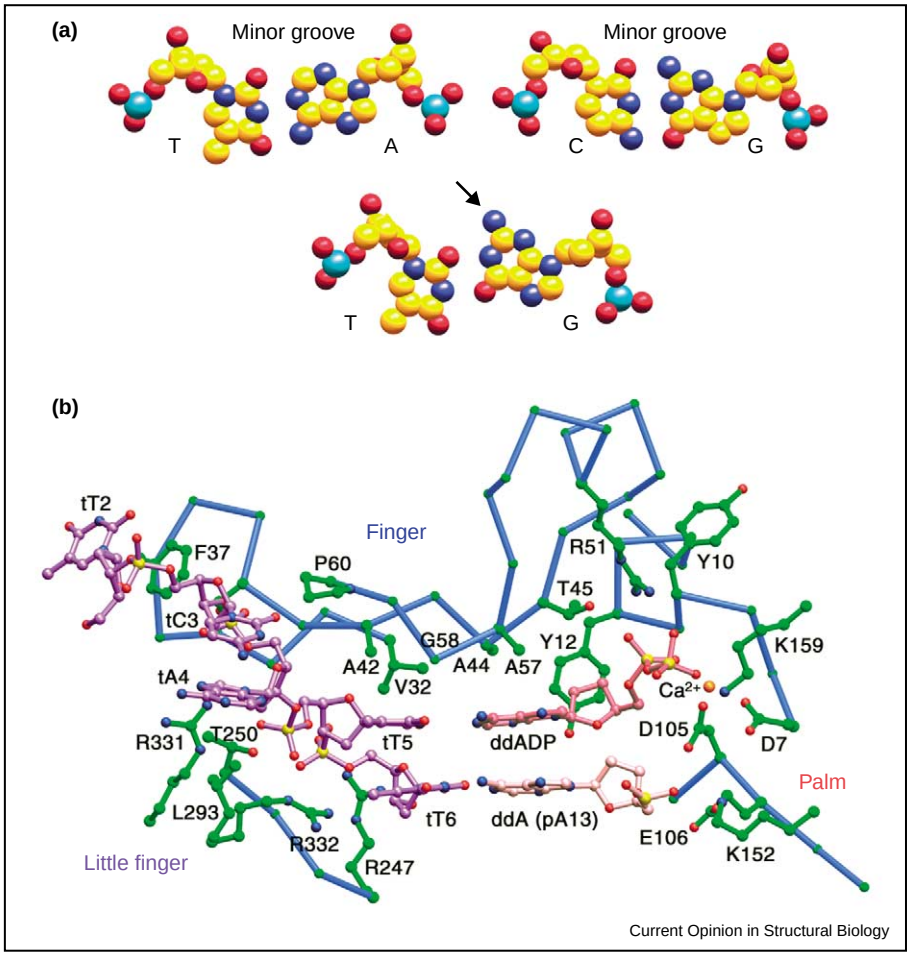
might also enable Dpo4 to accommodate bulky adducts in DNA.

Another peculiarity of the Y-family polymerases is the lack of a definitive conformational change in the finger domain in response to binding the incoming nucleotide that forms a Watson–Crick base pair with the template base. The protein-alone structure of Dbh, which shares over 50% sequence identity with Dpo4, suggests that the finger domain is already in the 'closed' active instead of 'open' inactive conformation as compared with the A and B family polymerases (Figure 1b) [37•]. The Dpo4–DNA–incoming nucleotide ternary complex structures support the hypothesis that the finger and palm domains of Y-family polymerases maintain the active conformation even without DNA and nucleotide substrate [37•–39•,40••]. Although 'induced fit' was proposed on the basis of kinetic analyses of yeast Pol η [43], the conformational change detected may occur in regions outside of the active site or even in DNA (see discussion of little finger domain below). The lack of an 'induced-fit' conformational change surrounding the active site seems to remove another barrier to the ability to make mismatched base pairs by Y-family polymerases, resulting in low fidelity and translesion synthesis.

The non-conserved substrate recognition site

Interestingly, aside from the three catalytic carboxylates chelating the divalent metal ions and the residues interacting with the triphosphate moiety of an incoming nucleotide, protein residues interacting with the template base and incoming nucleotide are not conserved among the Y-family polymerases. The number, size and charge of the residues involved vary dramatically. For example, most of the residues interacting with the replicating base pair in Dpo4 (i.e. Val-32, Ala-42, Ala-44, Ala-57 and Gly-58; Figure 4b), are not conserved in Pol V, Pol η, ι or κ. In fact, mutating Ser-62 of human Pol η to Gly, the equivalent of Gly-58 of Dpo4, resulted in Pol η becoming more active in bypassing lesions [44]. It is hypothesized that the variation of residues in contact with the replicating base pair allows each polymerase to attain its selection of a specific lesion to bypass and a favorite nucleotide to incorporate.

Figure 4



A mechanism for error-prone and translesion synthesis. **(a)** The difference between Watson–Crick and mismatched base pairs. The minor groove is smooth if base pairing is correct and jagged otherwise. For example, the N2 amine group of guanine (indicated by a black arrow) protrudes into the minor groove in a T:G mismatch. **(b)** The open and spacious active site of Dpo4. The protein backbone trace is shown in blue, sidechains contacting DNA are shown in green, DNA template is in purple, and the primer and incoming nucleotide in pink.

The unique little finger and its role

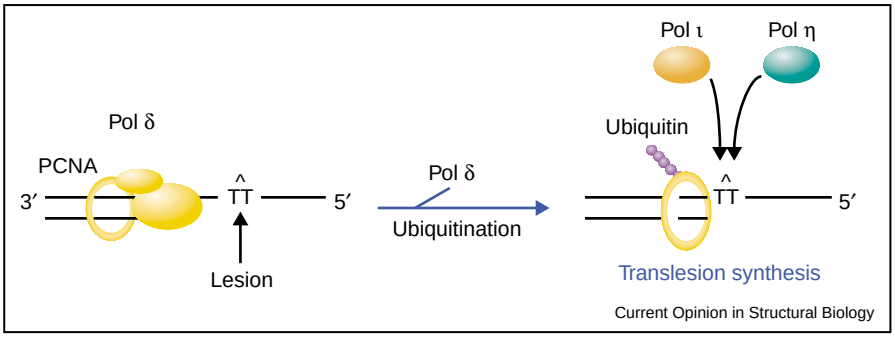
The little finger domain unique in the Y-family polymerases serves a special function. Because of the small thumb and finger domains, the interface formed between the catalytic core and DNA buries less than 600 $Å^2$ molecular surface, which is much smaller than the 1000 $Å^2$ buried by a conventional polymerase in the A or B family. In the Pol β (X-family), whose catalytic core is as small as or smaller than a typical Y-family polymerase, the lyase domain makes extensive interactions with the downstream DNA duplex and increases the overall protein–DNA interface [29]. The little finger domain of the Y-family polymerases plays a similar role and facilitates DNA association by interacting with the upstream DNA duplex (Figure 2).

The little finger domain is very diverse in amino acid sequence but structurally conserved within the Y-family (Figure 3). It contains a four-stranded β sheet and two parallel helices, and the β sheet fits in the DNA major groove with the two outermost strands interacting with the DNA backbones (Figure 2b). In the absence of DNA, this domain, which is distant from the active site, is mobile and cleavable by limited protease digestion [40••]. In the presence of a distorted and thus unsuitable DNA substrate, this domain moves out of the DNA major groove and reduces the overall protein–DNA contact (Ling and Yang, unpublished data). The flexibility of the little finger domain probably allows DNA to translocate between successive rounds of polymerization and possibly enables Dpo4 to optimize the enzyme–substrate interface for the nucleotidyl-transfer reaction.

Coordination of multiple DNA polymerases

Expression of Y-family polymerases is often induced by DNA damage. The relative amount of different poly-

Figure 5



A proposed mechanism for translesion DNA synthesis. A simplified replication fork, consisting of PCNA (big yellow ring) and Pol δ (two subunits), is stalled when encountering a DNA lesion, for instance, a TT dimer. Damaged DNA also activates Rad6 to mediate PCNA modification by ubiquitin and SUMO; modified PCNA then recruits the lesion bypass Y-family polymerase Pol η and Pol ι to carry out TLS.

merases can influence which polymerase gains access to a replication fork [14•]. In addition, specific accessory proteins are needed for Y-family polymerases to replicate DNA efficiently. RecA, which is also an SOS responsive protein, has been shown to be required in addition to single-strand-DNA-binding protein (SSB), β-clamp and clamp loader for *E. coli* Pol V to synthesize DNA through a TT dimer or 6–4 photoproduct [4,45,46]. Functional studies indicate that the C-terminal peptides of DinB homologs and Pol η interact with proliferating cell nuclear antigen (PCNA), the sliding clamp associated with DNA replication [4,41,42•,47•,48]. The corresponding C-terminal 12 residues in Dpo4 are disordered even when complexed with a DNA substrate [40••] and might become ordered when bound to PCNA. Recently, it has been shown that UV-induced or chemical damage to DNA leads to modification of PCNA by ubiquitin and small ubiquitin-related modifier (SUMO), which in turn leads to recruitment of DNA damage repair agents to the lesion sites [49,50••]. It is thought that Y-family polymerases might gain access to the DNA replication fork through ubiquinated-PCNA and replace a stalled replicative polymerase to complete translesion synthesis (Figure 5).

Conclusions

The crystal structures of the Y-family polymerases have revealed their resemblance to other DNA polymerases but with unique features that rationalize their ability to carry our low fidelity and translesion DNA synthesis. Elucidation of the specific mechanism by which each member of the Y family bypasses a specific lesion or makes a particular nucleotide incorporation awaits future structural studies of polymerases complexed with different DNA lesions. The finding of DNA damage-induced ubiquitination and SUMO modification of PCNA provides a steppingstone toward understanding the coordination of DNA replication and damage repair processes. Future studies are needed to address the consequence of single and multiple ubiquitination and SUMO modification of PCNA and to identify other factors that mediate the activation of DNA repair polymerases.

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