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Eukaryotic DNA polymerase ζ

Alena V. Makarova[a,b], Peter M. Burgers[a,*]

[a] Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, St. Louis, MO 63110, USA
[b] Institute of Molecular Genetics, Russian Academy of Sciences (IMG RAS), Kurchatov Sq. 2, Moscow 123182, Russia

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ABSTRACT

This review focuses on eukaryotic DNA polymerase ζ (Pol ζ), the enzyme responsible for the bulk of mutagenesis in eukaryotic cells in response to DNA damage. Pol ζ is also responsible for a large portion of mutagenesis during normal cell growth, in response to spontaneous damage or to certain DNA structures and other blocks that stall DNA replication forks. Novel insights in mutagenesis have been derived from recent advances in the elucidation of the subunit structure of Pol ζ. The lagging strand DNA polymerase δ shares the small Pol31 and Pol32 subunits with the Rev3–Rev7 core assembly giving a four subunit Pol ζ complex that is the active form in mutagenesis. Furthermore, Pol ζ forms essential interactions with the mutasome assembly factor Rev1 and with proliferating cell nuclear antigen (PCNA). These interactions are modulated by posttranslational modifications such as ubiquitination and phosphorylation that enhance translesion synthesis (TLS) and mutagenesis.

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1. Introduction

In the 1960s it was discovered that DNA damage induced mutagenesis is not a passive process in cells, but it arises as a result of enzymatic processes required the participation of several proteins [1–4]. These early bacterial studies were quickly followed up with studies in budding yeast, identifying several genes that were associated with a deficiency in mutagenesis after UV irradiation and treatment by chemical DNA damage agents [5–9]. Mutations in these genes demonstrated a reduced ability to undergo UV-induced reversion of the ochre-suppressible *argl-17* allele, and are therefore called *REV* genes (*reversionless*). The REV genes include *REV1*, *REV3* and *REV7*. The *REV3* gene was shown to be required for the generation of as much as 96% of UV-induced mutations in yeast [6], as well as about half of spontaneous mutations [10]. The *REV3* gene encodes the catalytic subunit of DNA polymerase ζ (Pol ζ), the enzyme involved in mutagenic replication of damaged DNA [11,12]. The *REV3*-dependent damage-induced mutagenesis pathway is evolutionarily conserved in all eukaryotes [13]. However, while *REV3* is dispensable in yeast, deletion of the mouse *REV3L* gene causes embryonic lethality, revealing the essential role of Pol ζ in mammalian development [14,15]. In this review, we will discuss novel insights in the subunit structure and architecture of Pol ζ, its DNA polymerase activity on undamaged and damaged DNA templates, its role in mutagenesis provoked by specific DNA damaging agents, and the regulation of its activity.

2. Structure of Pol ζ

The *Saccharomyces cerevisiae REV3* gene was isolated in 1989 and predicted to encode protein of Mr ~173 kDa with a sequence characteristic of DNA polymerase [11]. The human *REV3* gene encodes a protein of Mr ~353 kDa, about twice the mass of yeast protein [16]. The strong similarity in phenotypes of mutations in the yeast *REV3* and *REV7* genes indicated a possible functional collaboration of the Rev3 and Rev7 proteins. Indeed, in 1996 a heterodimeric complex of Rev3 and Rev7 was purified from yeast and characterized as the sixth eukaryotic DNA polymerase, Pol ζ [12]. Rev3 is a B-family DNA polymerase, like the catalytic subunits of the replicative polymerases, Pol α, Pol δ, and Pol ε [17]. However, Pol ζ lacks 3′-5′-exonucleolytic proofreading activity [12].

The small Rev7 subunit (Mr ~ 28 kDa) was shown to stimulate the catalytic activity of Rev3 by 20–30 fold, suggesting that this two-subunit complex was the minimal assembly required for Pol ζ activity *in vitro* [12]. Rev7 is a member of the HORMA (Hop1, Rev7, and Mad2) family of proteins [18]. The interaction between Rev3 and Rev7 had been mapped to a region N-terminal of the polymerase domain in Rev3 [12,19,20] (Fig. 1). The Rev7 subunit also plays an important role in mediating interactions of Pol ζ with other proteins. In particular, Rev7 interacts with the Rev1 DNA polymerase, which is also an essential component of the damage-induced mutagenesis machinery [5,19,21–23]. Rev7 also interacts

* Corresponding author. Tel.: +1 314 362 3872; fax: +1 314 362 71831.
E-mail address: burgers@biochem.wustl.edu (P.M. Burgers).

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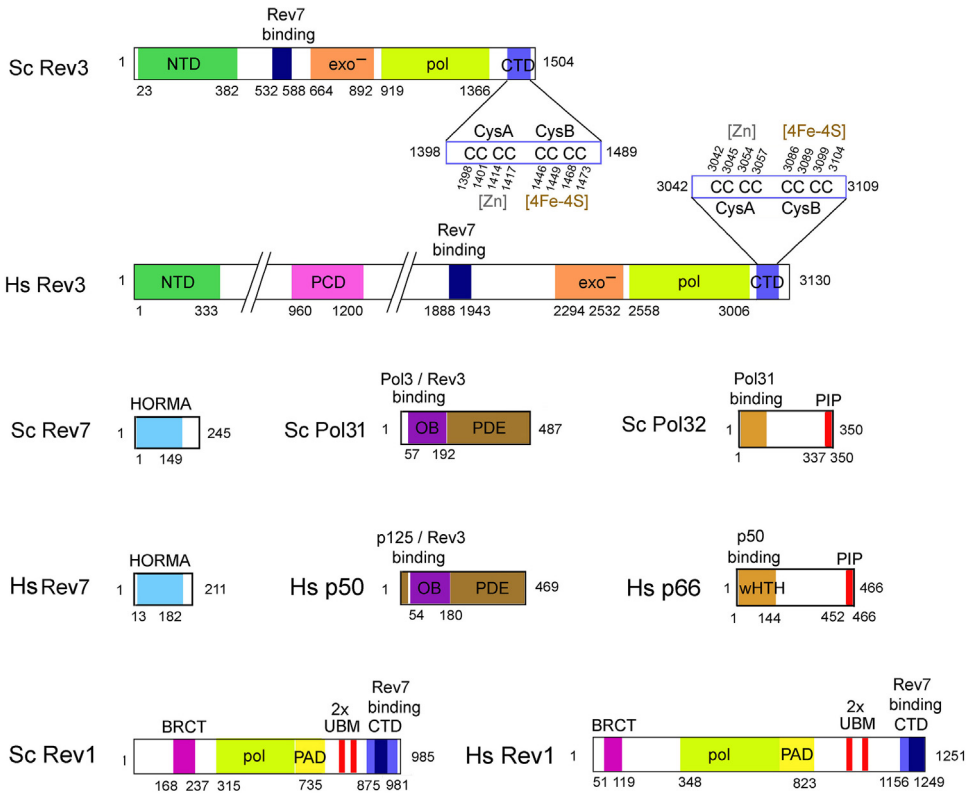

Fig. 1. Structural organization of Pol ζ and Rev1. The domain structure of *S. cerevisiae* and human Pol ζ and Rev1 are shown. Subunit–subunit interaction motifs and interactions with (ubiquitinated) PCNA are indicated. NTD – N-terminal domain, CTD – C-terminal domain, exo – inactive 3′–5′ exonuclease domain [11,12], pol – DNA polymerase domain, PCD – positively charged domain [16,37], HORMA – Hop1, Rev7, and Mad2 family domain [18], OB – oligonucleotide–oligosaccharide binding fold [36], PDE – phosphodiesterase domain [36], oligonucleotide–oligosaccharide binding fold PAD – polymerase associated domain [149], BRCT – BRCA1C terminal domain [150], PIP – PCNA-interacting motif [151], UBM – ubiquitin binding motif [103,107]. Conservative Cys residues coordinating [Zn] and [4Fe–4S] clusters [32].

with the Cdc7-Dbf4 protein kinase (DDK) [24]. DDK is both essential for the initiation of DNA replication and for UV-mutagenesis [25]. Human Rev7 also interacts with transcription factor TFII-I [26]. Finally, Rev7 interacts with the spindle assembly checkpoint protein MAD2, suggesting a potential link between TLS and chromosome segregation [27].

In 2012, several groups demonstrated that, like the other three B-family polymerases, Pol ζ is a multisubunit complex [28–30]. These four eukaryotic DNA polymerase complexes (Pol α, δ, ε, and ζ) are characterized by the presence of a cysteine-rich C-terminal domain (CTD) in each of their catalytic subunits [31]. The N-terminal cysteine-cluster (CysA) has been proposed to bind zinc, whereas the C-terminal cluster (CysB) has been proposed to contain an iron–sulfur cluster [31,32]. The CysB motif of Pol3 is required for the interaction of Pol3 with its second subunit Pol31 [32,33], which in turn binds Pol32 [34–36]. The CTDs of Pol3 and Rev3 show very high sequence homology, suggesting that the interaction between Rev3 and Pol31 could be analogous to that between Pol3 and Pol31. Indeed, the four-subunit Pol ζ_4 complex was shown to be organized by interactions between Rev3 and Pol31, and between Pol31 and Pol32 [28–30,37]. Mutations in the CysB motif of Rev3 CTD disrupted Rev3–Pol31 interaction and resulted in a complete defect in damage induced mutagenesis in yeast [28,30].

The Pol31 and Pol32 accessory subunits play important roles in Pol ζ function *in vitro* and *in vivo*. The purified human and yeast Pol ζ_4 complex demonstrated ~5–10-fold and 30-fold increase in biochemical activity, respectively, and showed enhanced processivity in comparison to the Pol ζ_2 enzyme [30,37]. Moreover, the Pol31 and Pol32 subunits were shown to be required for PCNA-dependent TLS by Pol ζ [30]. However, Pol δ and Pol ζ show important differences in complex stabilities with regard to their Pol32 subunit. Deletion of the yeast *POL32* gene does not result in lethality, however, *pol32Δ* strains show defects in DNA replication, are sensitive to replication inhibitors and DNA damaging agents, and are completely defective for UV- and MMS-mutagenesis [38,39]. In *pol32Δ* mutants, a functional Pol3-Pol31 complex is still formed, but it shows reduced functionality in DNA replication [34,40,41]. In contrast, the Rev3–Pol31 interactions are dependent on the presence of Pol32, and therefore *pol32Δ* mutants, like *rev3-cysB* mutants, only produce the two-subunit Rev3–Rev7 form of Pol ζ [30]. Because both *rev3-cysB* and *pol32Δ* mutants are defective for mutagenesis, a plausible explanation for the mutagenesis defect of *pol32Δ* is that the 2-subunit complex is inactive in this process. However, additional contributions by Pol δ to some forms of TLS that are abrogated in the *pol32Δ* mutant may also exist.

A 3D structural model of yeast Pol ζ_4 based on electron microscopy reconstruction has been proposed [20]. With regard to its structural architecture, Pol ζ shows some similarities with high-fidelity replicative DNA polymerases [31,42,43]. The Pol ζ_4 model suggests an elongated bilobal architecture with separate catalytic and regulatory modules. The Rev3 catalytic core forms a large lobe which is connected to a small regulatory lobe of accessory subunits Rev7, Pol31 and Pol32 *via* a long linker. However, even though Pol ζ and Pol δ share the Pol31–Pol32 accessory subunits, a detailed comparison between their architectures reveals differences that may underlie their different functions in the cell. As mentioned above, Pol3 forms a stable complex with Pol31 alone [40], but Rev3 does not [30]. One possible explanation for the Pol32 requirement in forming a stable Pol ζ complex is that the Rev7 subunit interacts with the C-terminal region of Pol32 [20]. Therefore, Pol32 may contribute to complex stability through dual interactions with Rev7 and Pol31. Surprisingly, in a departure from the consensus view of

the essentiality of the Pol ζ_4 complex for mutagenesis that followed from genetic and biochemical studies, a recent study by Siebler *et al.* showed that a *REV3* mutant lacking its entire CTD shows low but significant mutagenesis [44]. This mutagenesis is dependent on the catalytic activity of Rev3 and on the presence of both Pol32 and Rev1, as well as PCNA ubiquitination. Interestingly, this mutant shows maximal mutagenesis at low doses of UV light, and is defective at higher doses that show maximal mutagenesis in wild-type strains. That phenotype resembles the mutagenesis phenotype of a *pol32-ΔPIP* in which the PCNA-interaction motif has been deleted [45]. One possible explanation for these paradoxical results is that the Rev7–Rev3ΔCTD complex retains residual interactions with Pol32 through binding to Rev7 [20].

3. Human *REV3L* and Pol ζ

The damage-induced mutagenesis pathway is evolutionarily conserved from yeast to mammals [46]. The human *REV3L* gene encodes a protein about twice the mass of yeast Rev3 [16]. As expected, the proteins show high homology in both the polymerase and the cysteine-rich carboxy-terminal domains, as well as limited homology in the N-terminal domain (NTD) (Fig. 1). However, a ~280 aa spacer region between the NTD and the exonuclease domain (Exo) in yeast Rev3 has been expanded to ~2000 aa in Rev3L. This part consists of mostly unstructured and low complexity regions, but it also contains the Rev7 binding domain and a positively charged domain (PCD), which is unique to vertebrate species (Fig. 1). Deletion of ~800 aa of this internal region while retaining the PCD and the Rev7-binding domains, allowed the expression and purification of the human Pol ζ_4 complex [37]. This form has a subunit composition and biochemical properties similar to the yeast enzyme. The roles of the intervening inserts and the PCD remain to be determined.

Multiple experiments indicate that human Pol ζ has a similar cellular function to that of the yeast enzyme [16,47,48]. However, unlike yeast *REV3*, which is not essential for viability [11], disruption of *REV3L* in mice causes embryonic lethality revealing an important role of Pol ζ in cell proliferation and genomic stability even in the absence of environmentally induced damage [14,15,49]. Rev3-deficient embryos have retarded growth and die around mid-gestation. They demonstrate impaired mesoderm maintenance and a lack of hematopoietic cells [15]. They also accumulate double-stranded DNA breaks, chromosome translocations and show generalized p53-independent apoptosis [50,51].

The key function of Pol ζ in maintaining genome stability was further demonstrated in mice models with conditional and tissue-specific *REV3L* gene knockouts and downregulation of Rev3L mRNA. Conditional knockouts in adult mice enhanced spontaneous tumorigenesis [52]. Mice with epidermal disruption of *REV3L* developed skin tumors and failed to mount skin-regenerative responses [53]. Keratinocytes isolated from these mice demonstrated an increased UV sensitivity, accumulated DNA breaks and showed striking proliferation defects. Furthermore, mice expressing antisense transcripts to Rev3L mRNA show a reduction in somatic hypermutations in the IgV_H genes, suggesting that mutagenesis by Pol ζ is also required for robust immune development [54].

A tumor suppressor role for Pol ζ has also been indicated from studies in humans. A reduction of *REV3L* gene expression is associated with colon carcinomas [55]. A polymorphism in the 3′UTR of *REV3L* potentially affecting miRNA-mediated gene regulation contributes to lung cancer susceptibility [56]. Furthermore, Pol ζ is an important determinant for tumor resistance to chemotherapeutic agents in several types of human cancers [48,57–60]. Pol ζ is considered as a potential biomarker of chemoradiation resistance [61]. Testing of Pol ζ expression and its activity in patients may provide important diagnostic information and guide to a personalized therapeutic approach in cancer therapy. In support of this, downregulation of *REV3L* expression significantly enhanced the sensitivity of human cancer cells to cisplatin therapy [58,62]. Therefore, Pol ζ represents a promising target for the treatment of chemotherapy-resistant tumors.

4. Activities and fidelity of Pol ζ during normal cell growth

Pol ζ plays a significant role in maintaining genome integrity by protecting cells from DNA damaging agents and reducing cytotoxicity, but it does so at the expense of increased mutations. Yeast cell death by UV-damage is primarily prevented by the nucleotide excision repair machinery and by the activity of Pol η, which carries out TLS of UV-dimers in a relatively error-free manner [63,64]. However, while Pol ζ activity contributes much less to the viability of UV-irradiated cells than Pol η does [63], Pol ζ is responsible for as much as 96% of mutations that are induced by UV irradiation [6]. Importantly, Pol ζ also is responsible for about half of spontaneous mutations [6,10]. These latter studies suggest that Pol ζ is a low fidelity enzyme compared to the other B-family DNA polymerases. Indeed, while an exonuclease domain can be identified in Rev3, Pol ζ lacks 3′–5′ exonuclease proofreading activity [12]. Steady state kinetic analyses of dNTP incorporation and misincorporation by yeast Pol ζ on oligonucleotide substrates showed a robust discrimination (10^3–10^4 fold) against incorporation of the incorrect nucleotide on base-paired template-primers. However, Pol ζ showed only a 10–100 fold discrimination against extension of mismatched over matched template-primer termini [65]. Furthermore, the enzyme readily extended from primer termini positioned opposite template 8-oxoguanine or O6-methylguanine residues [66]. Based on these types of studies, Pol ζ has been designated as an extender polymerase during TLS, designed to elongate primer termini that are positioned opposite base damage and non-instructional lesions.

Fidelity measurements of replication by Pol ζ on gapped plasmid DNA substrates in which many different sequence contexts were sampled, demonstrated a low fidelity of Pol ζ with single base substitution error rates of $\sim 10^{-3}$ [67]. These error rates are lower than those by Y-family DNA polymerases but much higher than those of replicative B-family DNA polymerases. Pol ζ is prone to generating A-dCMP, C-dCMP and G-dGMP mismatches *in vitro*. Consistently with these data, C–G to G–C transversions were shown to be a characteristic of Pol ζ mutagenesis *in vivo* [68,69]. Pol ζ also generates multiple single base errors clustered in short patches within 6–10 nucleotides. These complex mutations occur both *in vitro* [67] and *in vivo* [70–74]. The frequency of such complex mutations far exceeds that would be predicted based on the mutation rates for single mutations alone indicating that the first error increases the probability of additional errors. This indicates that Pol ζ contributes to mutagenesis *in vivo* by directly generating its own mismatches and then extending them.

These conclusions were underscored by the study of the L979F mutator allele of *REV3* in yeast that increases the mutation rate *in vitro* 5-fold compared to wild-type [75]. In yeast, the *rev3-L979F* mutant caused a 2–3 fold increase in spontaneous mutation rates and a several fold increase in UV-induced mutation rates [69,76]. The spectrum of mutations, in particular tandem base-pair and complex clustered mutations that are produced in yeast, when compared to those produced *in vitro*, strongly suggest that Pol ζ can perform mutagenic bypass of lesions during which it synthesizes processively a short track of error-prone DNA.

The role of Pol ζ in spontaneous mutagenesis can be explained the involvement of Pol ζ in the bypass of spontaneous damage in the cell. The increase in spontaneous mutations in the

Table 1
TLS activities of Pol ζ *in vivo* and *in vitro*.

DNA damage	Organism	Pol ζ TLS *in vivo*	Pol ζ TLS *in vitro*
Abasic sites	Yeast	Participates in mutagenic TLS opposite AP-sites [87,132,133]	Bypasses AP-sites [82] Bypass is stimulated by PCNA [30,78]
	Human		Yeast Pol ζ cooperates with hPol ι and hPol η to bypass AP-sites [83,134]
Photo-products	Yeast	Mediates survival and mutagenesis after UV irradiation [6], bypasses T–T (6–4) but not T–T cis-syn photoproducts [87]	Bypasses cis-syn T–T dimers and T–T (6–4) photoproducts alone in [12,82], stimulated by PCNA [78]
	Human	Mediates survival and mutagenesis after UV irradiation [16,47,135]	Yeast Pol ζ cooperates with hPol ι and hPol η to bypass T–T (6–4) photoproducts [83]
Ionizing radiation and oxidative stress	Yeast	Mediates mutagenesis induced by ionizing radiation [8], participates in TLS opposite thymine-glycols [83]	Bypasses thymine-glycol with relatively high fidelity [83]; as primer termini extender yeast Pol ζ cooperates with Pol δ to bypass 8-oxo-G and O^6-meG [66]
	Human	Mediates mutagenesis induced by 8-oxo-dGTP [136]	Yeast Pol ζ cooperates with hPol ι to bypass 8,5'-cyclopurines [137]
Chemical carcinogens	Yeast	Mediates mutagenesis induced by 4-NQO and MMS [7,9], mediates mutagenic TLS opposite 3-meA [138]	Bypasses AFB1-N7–dG adducts with high fidelity and AFB1-FAPY–dG adducts with low fidelity [84,85], cooperates with Rev1 to accurately bypass N2 minor groove γ-HOP–dG adducts [139], bypasses AAF–dG adduct with low accuracy [80]
	Human	Mediates mutagenesis induced by BPDE [47]	Yeast Pol ζ cooperates with hPol η to bypass butadiene-derived uridine adducts [140]
Interstrand crosslinks	Yeast	Mediates cis-platin and hexavalent chromium toxicity and mutagenesis [141,142]; required for ICL repair [141]	
	Human, frog	Mediates cisplatin cytotoxicity and mutagenesis [48]	Xenopus Pol ζ required for ICL bypass [143]

rev3-L979F mutator mutant is consistent with this explanation [69]. In addition, however, Pol ζ is recruited to sites of replication fork stalling when replisomes themselves are compromised. Most of the mutagenesis that is associated with mutant forms of Pol δ or Pol ε that have decreased stability or functionality, is dependent on Pol ζ [73,77]. This mutagenesis has been called DRIM for defective replisome-induced mutagenesis [73].

Compromised replisomes are expected to stall more frequently at non-B DNA structures, and in particular at short inverted repeats forming hairpin structures. These sites were shown to activate Pol ζ during DRIM [74]. The sites of replicative polymerase stalling at non-B DNA structures are associated with the high proportion of GC–CG transversions and complex mutations. Error-prone bypass of non-canonical DNA structures by Pol ζ often occurs *via* template-switching DNA synthesis and subsequent DNA strand realignment, followed by extension of mismatched primer termini by Pol ζ [74]. Exposure of yeast cells to the replication inhibitor hydroxyurea that results in depletion of the dNTP pool also causes a Pol ζ-dependent increase in mutagenesis [73]. The involvement of Pol ζ in the replication of non-damaged DNA after replication fork stalling may prevent the formation of double-stranded breaks and associated chromosome instability, at the cost of increased mutations.

5. The role of Pol ζ in TLS and damage induced mutagenesis

Genetic and biochemical studies have demonstrated that Pol ζ is involved in TLS and mutagenesis in response to a large variety of DNA damages. These studies are summarized in Table 1. Biochemical studies have shown that the TLS activity of the 4-subunit Pol ζ_4 is much more efficient than that of Pol ζ_2 [30,37], and additionally, that PCNA further enhances the bypass activity of Pol ζ_4 [30,78]. These considerable differences in biochemical properties of the different assemblies may explain why some investigators observed no or inefficient bypass of certain damages, such as abasic sites or pyrimidine dimers [79–81], whereas other investigators detected efficient bypass of the same types of DNA damage [12,30,37,78]. In addition, the efficiency of TLS by Pol ζ depends on the sequence context in which the lesion resides [82].

Pol ζ shows a high fidelity for the bypass of some lesions such as thymine glycol [83] and aflatoxin-derived N7–dG adducts [84], but low fidelity opposite other lesions, such as aflatoxin-derived FAPY–dG adducts [85]. For some damages such as T–T (6–4) photoproducts, other DNA polymerases such as Pol ι are more proficient at the insertion step across damage *in vitro*, while Pol ζ is more proficient in the extension step [83]. Which DNA polymerase actually carries out bypass synthesis of a specific form of UV damage has been studied in yeast by determining the exact sequence contexts of TLS in informative polymerase mutants [86]. In addition, complementary studies have been carried out by transforming yeast, or transfecting human cells with DNA plasmids containing that specific damage. In yeast, these experiments show a strong dependence on Pol ζ, particularly for pyrimidine dimers transformed into a mutant Pol η background [87,88]. However, in human cells they also indicate the involvement of other TLS polymerases such as Pol κ and Pol ι [89–91]. Therefore, whether a two-polymerase bypass mechanism operates during TLS may not only depend on the type of damage but also on the organism. Mammals, with their wealth of specialized bypass DNA polymerases may be more likely to use two-polymerase mechanisms than yeast, which only has the Pol η, Pol ζ and Rev1 TLS enzymes.

Mammalian Rev1, which is considered the scaffold on which the mutasome is built, has been shown to simultaneously interact with Pol ζ and with one of the several Y-family DNA polymerases (Pol η, κ, or ι), which may facilitate multi-polymerase TLS [21,92–94]. However it is not clear whether yeast Rev1–Pol ζ and Pol η (yeast has no Pol κ or Pol ι) are present in one complex. One group reported an interaction between the little finger domain of Rev1 and Pol η [95]. However, another group failed to detect an interaction between these two yeast proteins while the interaction between the mammalian orthologs was readily observable [93].

6. Regulation of mutagenesis

Mutagenesis is regulated at several levels, including by post-translational modifications (Table 2). The observation that Pol3 and Rev3 share the Pol31–Pol32 subunits has led to the proposal

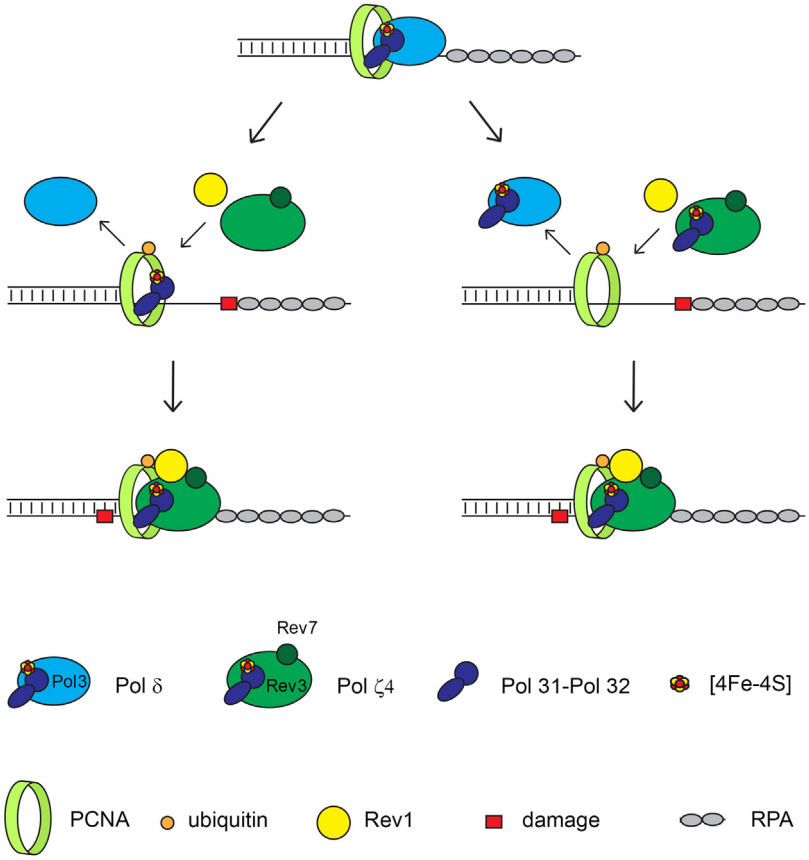

Fig. 2. Two models for Pol ζ recruitment to DNA damage sites. See text for details.

of a model in which Pol3 and Rev3 switch binding to damaged DNA-associated Pol31–Pol32 during TLS [28] (Fig. 2). In this model, stalling of Pol δ at sites of damage induces dissociation of Pol3 from Pol31–Pol32 leaving the latter associated with the sites of damage, and thereby marking it for subsequent association of Rev3–Rev7, in order to facilitate TLS. In support of this model, studies of the stability of Pol δ after DNA damage have shown that the Pol3 subunit, but not Pol31–Pol32, is partially degraded in response to DNA damage [96]. It remains to be determined whether the Pol3 that is degraded is part of the soluble pool or chromatin-bound Pol3. The latter would be consistent with the model. Degradation is dependent on Def1, a ubiquitin-binding protein that previously had been identified as important for stimulating the proteasome-mediated degradation of RNA polymerase II after DNA damage, thereby promoting the efficiency of transcription coupled nucleotide excision repair [97]. A *def1Δ* strain is defective for damage-induced mutagenesis, suggesting that Pol3 proteolysis may be involved in a polymerase switch mechanism [96] (Fig. 2).

However the switching hypothesis does not explain how Pol ζ operates during TLS on the leading strand which is replicated by Pol ε [98,99]. In fact, if the switching hypothesis is correct, the implication would be that it is relegated to post-replicational gap filling synthesis, at least on the leading strand. Furthermore, the switching hypothesis also suggest the existence of the two-subunit form of Pol ζ, which only assembles into a four-subunit enzyme with Pol31–Pol32 at sites of DNA damage, from which Pol3 has previously been displaced. Instead, experiments in yeast indicate that a stable Pol ζ_4 complex exists in all phases of cell cycle, and imposing DNA damage does not alter the stability of a complex [30].

Table 2
Yeast genes required for mutagenesis.

Yeast gene	Function	References
REV1	Deoxycytidyl transferase and mutasome organizer; binds Rev7 and ubiquitinated PCNA.	[21,23,94,107,110,111,144,145]
REV3	Catalytic subunit of Pol ζ.	[11,12]
REV7	Accessory subunit of Pol ζ	[12]
POL31/POL32	Accessory subunits of Pol ζ and Pol δ; Pol31 binds Rev3, Pol32 binds Rev7 and PCNA.	[20,28–30,34,45]
POL30	PCNA, the DNA sliding clamp and processivity factor, interacts with Pol32 and with Rev1	[45,106,107,110,111,146,147]
RAD6/RAD18	E2/E3 that mono-ubiquitinates PCNA	[100,101]
RAD5	Involved in poly-ubiquitination of PCNA. Required for mutagenesis in some studies, but not in others.	[71,88,114–118,121,148]
DEF1	Enhancer of ubiquitination for degradation; destabilizes Pol3 after damage.	[96,97]
CDC7/DBF4	Cell cycle protein kinase (DDK) in replication initiation; required for mutagenesis.	[24,25,119]
MEC1/DDC2	Checkpoint kinase, ortholog of ATR/ATM; required for mutagenesis in nucleotide-excision-repair defective mutants.	[125]
RAD17/MEC3//DDC1-RAD24	DNA damage 9-1-1 checkpoint clamp/clamp loader; required for mutagenesis in nucleotide-excision-repair defective mutants.	[122,127]

The DNA sliding clamp and processivity factor PCNA is a key regulator of Pol ζ activity. PCNA can contact Pol ζ through its Pol31/Pol32 accessory subunits. The functional interaction of Pol ζ with PCNA stimulates its DNA polymerase activity and DNA translesion synthesis [30,78]. *S. cerevisiae* Pol ζ interacts with PCNA through PCNA-interaction motif at the C-terminus of Pol32 and deletion of this motif attenuates PCNA-dependent TLS by Pol ζ *in vitro* [30], and damage-induced mutagenesis *in vivo* [45]. However, this Pol32 truncation only marginally affects PCNA-dependent replication by Pol δ [45]. Moreover, unlike other polymerases, Pol ζ binds a region of PCNA that is located near the monomer–monomer interface, and this interaction in disrupted in mutagenesis-defective PCNA mutants [30,77]. The utilization of different PCNA-binding modes by Pol ζ and Pol δ may underlie differences in the regulation of their activities *in vivo*.

Mutagenesis is regulated by ubiquitination of PCNA [100,101]. The damage-response ubiquitin conjugating-ligase heterodimer Rad6–Rad18 mono-ubiquitinates PCNA when excessive RPA-coated ssDNA is formed in response to DNA damage and replication fork stalling [102]. Mono-ubiquitinated PCNA shows an increased interaction with Rev1 [103,104]. Rev1 has both a PCNA and ubiquitin-binding domain, and mutations in either domain abrogate mutagenesis [105–107]. In contrast, Pol ζ does not show increased interactions with ubiquitinated PCNA [104], further emphasizing the essential role of Rev1 in mutagenesis.

Ubiquitin-binding motifs (UBMs) have not been found in any of the four Pol ζ subunits. Instead, mono-ubiquitination of PCNA likely exerts its TLS-promoting activity through Rev1. Rev1 interacts with PCNA through its BRCT-domain and through the polymerase-associated domain [106,108,109], and shows additional interactions with ubiquitinated PCNA through its UMB motif [107,110]. The affinity of Rev1 for mono-ubiquitinated PCNA is higher than that for unmodified PCNA, further emphasizing the essential role of Rev1 in mutagenesis [107,110,111].

In addition to Rad6–Rad18, other factors in the ubiquitin pathway are also required for mutagenesis, but their function is less well understood. Rad5 is important for mediating K63-linked poly-ubiquitination of PCNA by Mms2-Ubc13 in a damage tolerance pathway that controls error-free repair in a recombination-dependent manner [100,112,113]. Rad5 was shown to be important for UV-mutagenesis in a specific *arg4–17* reversion assay, but this activity was independent of the ubiquitin-ligase and helicase activities of Rad5 [114]. Rad5 is also important for the generation of mutations associated with the transformation of damage-containing plasmids in yeast [88,115]. In contrast, in a forwards mutation assay, *rad5Δ* mutants were proficient for UV-mutagenesis [116]. Furthermore, in mammalian cells, the two orthologs of Rad5, HTLF and SHPRH suppress UV- and alkylation-mutagenesis, respectively [117]. Damage-induced mutagenesis is actually enhanced in cells depleted for these orthologs. Likewise, mouse knock-out strains of HTLF and SHPRH are proficient for somatic hypermutation, a hallmark of damage-induced mutagenesis [118].

Phosphorylation also plays a major role in the regulation of mutagenesis. Mutations in the Cdc7 or Dbf4 genes, which constitute the DDK kinase that is essential for initiation of DNA replication, show a strong defect in damage-induced mutagenesis [24,25,119,120]. One phosphorylation target of DDK is the Rev7 subunit, but it remains to be established whether phosphorylation of Rev7 is the critical switch for mutagenesis, or whether there are other significant Cdc7-mediated modifications [24]. In addition, the DNA damage checkpoint is involved in efficient mutagenesis under certain conditions. First, the 9-1-1 checkpoint clamp is required for UV-mutagenesis in non-dividing cells [121]. Second, while the 9-1-1 clamp is dispensable for UV-mutagenesis in dividing cells, in nucleotide excision repair-defective mutants 9-1-1 becomes required for UV-mutagenesis [122]. The 9-1-1 clamp loads onto a primer/template DNA containing a 5′-junction, which is the opposite loading polarity of PCNA [123]. Therefore, it is unlikely that 9-1-1 acts by stimulating Pol ζ activity, but rather by activating Mec1 to phosphorylate an important target that stimulates TLS [124]. Rev1 is one proposed target for Mec1 phosphorylation, but the essential modifications have not yet been identified [125,126].

Spontaneous mutagenesis and DRIM (defective replisome induced mutagenesis) are largely subject to similar regulatory controls compared to damage-induced mutagenesis. Like UV-mutagenesis, DRIM is dependent on PCNA ubiquitination. However, sumoylation of PCNA also contributes to the efficiency of DRIM [77]. Spontaneous Pol ζ-dependent mutagenesis depends on the 9-1-1 checkpoint clamp [127].

The regulatory aspects of mutagenesis in this review have mostly focused on the yeast *S. cerevisiae*. The basic machinery that carries out TLS is conserved in mammals [37]. Furthermore, the regulatory controls are also conserved in mammals. These include PCNA ubiquitination, as well as phosphorylation by the checkpoint kinase ATR and by Cdc7 [128]. Additional steps also exist. Spartan is a conserved mammalian protein that appears to be absent from yeast. It interacts both with Pol δ and with ubiquitinated PCNA, and negatively regulates mutagenesis [129–131]. In human cells Spartan depletion facilitates the formation of a complex between Rev1 and Pol ζ and enhances damage-induced mutagenesis [130]. The human transcription factor TFII-I binds the Rev7 subunit of Pol ζ as well as PCNA, and is required for TLS and DNA damage tolerance [26]. However, the TLS function of TFII-I appears to be independent of its role in transcription.

7. Conclusion

In this review, we have discussed the role of the DNA polymerase activity of Pol ζ on undamaged and on damaged DNA, and the biological significance of low fidelity and TLS activity of Pol ζ. We have focused on the structural organization of the Pol ζ complex and the regulation of its activity in yeast and in human cells. Novel insights in mutagenesis have been derived from recent advances in the definition of the subunit structure of Pol ζ. Latest studies reveal that with regard to its structural architecture, Pol ζ demonstrates a high similarity with the multisubunit high-fidelity replicative DNA polymerases, however preserves unique structural features that distinguish this enzyme from those other B-family polymerases. There exists a wide spectrum of interactions between Pol ζ subunits and its various binding partners. In addition, there are essential roles for posttranslational modifications in the regulation of Pol ζ function. The complexity in forming a functional Pol ζ mutasome in cells shows that the cell maintains a strict control of its mutagenic activity. However, in addition it may reflect a flexibility of the TLS machinery in order to carry out successful DNA synthesis opposite different types of DNA lesions and replication fork-stalling structures *in vivo*. Many mechanistic aspects of these types of Pol ζ control, especially in human cells, remain largely unknown. Therefore, structural studies and analyses of the mechanisms of regulation of Pol ζ function are important areas for future research.

Conflict of interest

None declared.

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