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Review Article

# Polymerase iota - an odd sibling among Y family polymerases

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ABSTRACT

It has been two decades since the discovery of the most mutagenic human DNA polymerase, polymerase iota (Polι). Since then, the biochemical activity of this translesion synthesis (TLS) enzyme has been extensively explored, mostly through *in vitro* experiments, with some insight into its cellular activity. Polι is one of four members of the Y-family of polymerases, which are the best characterized DNA damage-tolerant polymerases involved in TLS. Polι shares some common Y-family features, including low catalytic efficiency and processivity, high infidelity, the ability to bypass some DNA lesions, and a deficiency in 3′→5′ exonucleolytic proofreading. However, Polι exhibits numerous properties unique among the Y-family enzymes. Polι has an unusual catalytic pocket structure and prefers Hoogsteen over Watson-Crick pairing, and its replication fidelity strongly depends on the template; further, it prefers $Mn^{2+}$ ions rather than $Mg^{2+}$ as catalytic activators. In addition to its polymerase activity, Polι possesses also 5′-deoxyribose phosphate (dRP) lyase activity, and its ability to participate in base excision repair has been shown. As a highly error-prone polymerase, its regulation is crucial and mostly involves posttranslational modifications and protein-protein interactions. The upregulation and downregulation of Polι are correlated with different types of cancer and suggestions regarding the possible function of this polymerase have emerged from studies of various cancer lines. Nonetheless, after twenty years of research, the biological function of Polι certainly remains unresolved.

## 1. Introduction

DNA polymerase iota (Polι), originally named as RAD30B, was discovered as the second human homolog of yeast Rad30 during a surge in translesion synthesis (TLS) polymerase discovery at the turn of the century [1]; its translesion activity was confirmed a year later [2–4].

Polι, together with polymerases eta (Polη), kappa (Polκ), and Rev1, belongs to the Y-family of polymerases, which are best recognized for their translesion synthesis (TLS) activity [5]. During TLS, a high fidelity replicase that is blocked by a DNA lesion is replaced by a TLS enzyme that, by itself or with help from another polymerase, introduces nucleotides opposite the lesion in the template and extends it to the point at which the replicase can take over (reviewed in [6–7]). Recruitment of TLS polymerases to blocked replication forks must be strictly controlled because Y-family polymerases, with their variable nucleotide selection and lack of 3′→5′ exonuclease activity, are highly error-prone when copying undamaged templates. Regulation of Y-family polymerases involves posttranslational modifications of various proteins and protein-protein interactions. A major regulatory role is played by the processivity replication factor PCNA, which undergoes monoubiquitination at K164 in response to blocked replication fork progression [8]. This monoubiquitination strengthens the interaction of PCNA with Y-family polymerases by providing an additional binding site, which helps initiate TLS [9].

Polι has typically been thought of as an error-prone backup for Polη based on the biochemical characterization of Polι, the hypermutable nature of xeroderma pigmentosum variant (XPV) cells lacking Polη, and the continued difficulties in identifying specific function for Polι. However, the unusual features of Polι and the increasing number of putative functions and known regulation of Polι suggest a specific, independent cellular role for Polι.

Despite multiple reviews on translesion synthesis and Y-family polymerases, including Polι, there are few articles focusing solely on Polι [7,10–21].

The aim of this review is to summarize findings about Polι from the last twenty years, especially those involving Polι expression and regulation, its ability or inability to bypass certain lesions, which are information that may help determine the cellular function of Polι.

## 2. Polι and its homologs

In humans, the *POLI* gene is localized on chromosome 18q21.2. Polι is evolutionarily conserved and its homologs are present in many organisms. Unlike other Y-family polymerases, homologs of Polι have not

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been identified in prokaryotes, yeast, or nematodes. However, Polι is present in a variety of other fungi excluding yeast, including members of both the Ascomycota and Basidiomycota phyla. Most of plants seem to lack *POLI* homologs. Nonetheless, sequences encoding Polι have been found in seven species of green algae and the spikemoss *Selaginella moellendorffii*, which belongs to an ancient group of plants. It has been speculated that *POLI* may have resulted from duplication of *POLH* (encoding Polη) shortly before the divergence of insects [22], as the enzymatic properties of *Drosophila melanogaster* Polι more closely resemble those of *Saccharomyces cerevisiae* Polη than human Polι [23]. In addition, orthologs of *POLI* gene have been identified in some mollusks and echinoderms, including the pacific oyster *Crassostrea gigas* and the purple sea urchin Strongylocentrotus purpuratus, which show 40-65% identity with human *POLI*. Surprisingly, Polι was not identified in chicken cells and it was previously thought that birds are deficient in this polymerase; however, additional genomic sequencing has revealed Polι in 50 species of birds. Nonetheless, the lack of Polι in certain species is intriguing and awaits explanation. Additionally, the analysis of crude tissue extracts from various vertebrates, including fish, amphibians, reptiles, birds, and mammals, demonstrated that the distinct Polι activity of incorporating G opposite template T only occurs in mammalian tissues [24]. This may indicate that in mammals, Polι possesses specific enzymatic activity correlated with structural changes in its active center, and L62 residue in human Polι appears responsible for this particular enzymatic property [24].

Polη is the closest paralog of Polι in mammalian cells, however, the Y family polymerases Polκ and Rev1 also share some homology with Polι, particularly within the catalytic domain. Despite high sequence similarity, overexpressed Polι is not able to complement defects in XPV cells caused by Polη loss [25].

## 3. Polι localization and tissue specificity

Human Polι is roughly 80-kDa protein consisting of 715 amino acids (GenBank Accession number AF140501.1). Some reference sequences (e.g. NM_007195.2) describe Polι as a 740 amino acid protein with an additional 25 residues at the N-terminus, however, experimental evidence suggests that the 715 amino acid form of Polι is the predominant isoform [26].

Polι is mainly a nuclear protein, although it can also localize to cytoplasmic bodies (www.proteinatlas.org, [27]). Polι possesses a non-classical nuclear localization signal that loosely maps to amino acids 219 to 451, with the region formed by amino acids 400-451 potentially being highly important for nuclear localization [25]. Polι is expressed at low or medium levels in various tissues and is most highly expressed in the testes [1] and thyroid glands at both the RNA and protein levels (www.proteinatlas.org, [28]). This is supported by biochemical analyses of crude cell extracts of various mammalian tissues, in which Polι activity was detected in testes and brain extracts [24]. Interestingly, Polι activity varies significantly during development, as high levels of Polι activity detected in extracts of most embryonic mouse organs decreased sharply after birth [29]. Moreover, varying levels of Polι expression have been observed in different types of tumors [30–34]. Particularly tight correlations between Polι expression and cancer incidence are observed for esophageal squamous cell carcinoma (ESCC) tissues and Polι is a proposed biomarker for the metastasis of ESCC tumors [35–36].

## 4. Polι structure and domains

Despite a lack of sequence homology, Polι, similarly to all DNA polymerases, topologically resembles a right hand with fingers (38-98 aa), thumb (225-288 aa), and palm (25-37 and 99-224 aa) subdomains that form a catalytic active site that is highly conserved among Y-family polymerases and is N-terminally located [37]. Similar to other Y-family polymerases and in contrast to classical replicases, Polι lacks a 3′→5′ exonuclease domain and possesses an additional sub-domain at the C-terminus of the catalytic core named the “little finger” (LF), “polymerase associated domain” (PAD), or “wrist” (298-414 aa) (Fig. 1) [11]. LF domains share little sequence identity across the Y-polymerase family and play important roles in defining the unique biochemical characteristics of particular Y enzymes [38]. Compared to other Y-family polymerases, the LF of Polι has greater mobility and may be responsible for the enzyme’s low processivity [39]. In general, for Y-family members, short fingers and thumb domains create a spacious and flexible catalytic pocket that enables tolerance of various damaged bases in templates and provides limited stringency in selection of upcoming nucleotides, causing increased infidelity when copying undamaged templates. Compared to other Y-family polymerases, the active site of Polι is rather narrow, which stimulates formation of non-canonical interactions between nucleotides. The palm domain, containing catalytic residues D34, D126, and E127 located at the bottom of the DNA binding groove, and the fingers domain that lays over the template base and the incoming nucleotide are critical for Polι activity [40–41]. The thumb domain makes a few contacts with the minor groove of DNA, while the LF domain makes multiple contacts with the major groove of DNA [18,41]. Additionally, the Y39 residue likely helps discriminate between ribo- and deoxyribonucleotides [18].

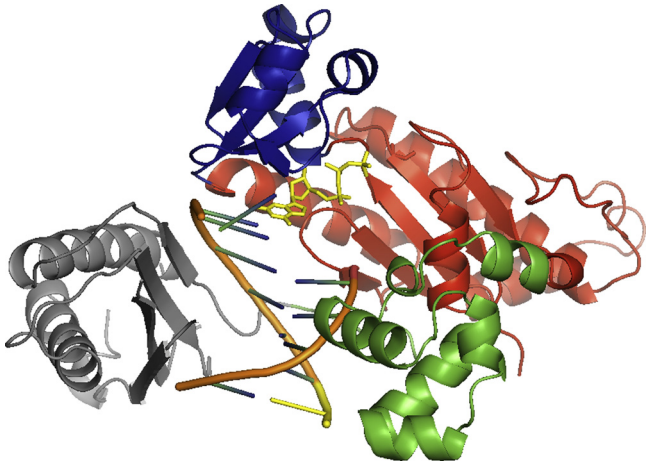

**Fig. 1.** Crystal structure of the catalytic domain of human Polι in a ternary complex with a T-G mismatch. Domains are color-coded as follows: palm (red), fingers (blue), thumb (green), LF (grey) (PDB ID code 3GV8) [42].

The N-terminal catalytic core of Polι contains two partly overlapping catalytic domains. The domain with DNA polymerase activity is located between 24-414 aa while the domain with dRP lyase activity is located between 79-445 aa [43]. In addition, the N-terminal region containing residues 1-78 may indirectly influence dRP lyase activity and residues Q59 and K60 may stabilize DNA in the correct orientation or help generate the protein conformation required for cleavage of dRP-groups [44].

The N-terminal, catalytic half of Y family polymerases appears to have a well-defined structure while the C-terminal half is predicted to mostly contain disordered regions except for short regions corresponding to protein binding domains [45], including a PIP box (PCNA-interacting peptide, 420-427 aa) [46–47], RIR (Rev1-interacting region, 539-554 aa) [48] and two UBMs (ubiquitin-binding motifs, 496-524 and 681-709 aa) [37,49–50] (Fig. 2). These C-terminal protein binding domains are involved in protein-protein interactions with important regulatory roles.

## 5. Biochemical properties of Polι

Like other Y family polymerases, Polι lacks 3′→5′ exonuclease activity [2–3]. However, this lack of proofreading activity does not fully

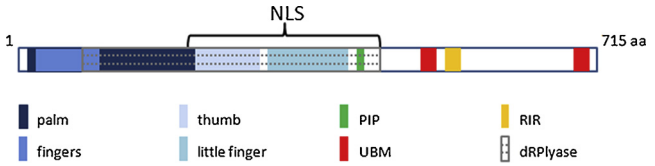


**Fig. 2. Domains of Polι.** The polymerase catalytic domain is contained within the palm, fingers, thumb, and little finger domains (different shades of blue) and partially overlaps with the dRP lyase domain (gray dotted lines). In addition, Polι contains a variety of domains involved in protein-protein interactions and nuclear localization signal (NLS).

explain the high and extremely template-dependent infidelity of Polι with undamaged DNA. Opposite template A Polι is the most accurate and misincorporates A, G, or C with a frequency of $10^{-4}$, which is moderate for Y- family polymerases. Opposite template G and C Polι is less accurate and misincorporates roughly one in 100-1000 nucleotides. Interestingly, the fidelity of Polι is lost opposite template T, with Polι exhibiting 3-10-fold higher incorporation of incorrect G compared to correct A [2–4]. This remarkable property is specific for mammalian Polι, as Polι from *Drosophila melanogaster* typically incorporates A opposite template T [23].

These dramatic differences in the efficiency and error frequency of Polι depending on the specific template base were initially explained by Washington et al. based on pre-steady-state kinetic analysis [51]. They showed that opposite template A, the correct nucleotide is preferred due to tighter binding and faster incorporation, and opposite template T the G misincorporation occurs due to tighter binding of G. In addition, based on structural analysis, interactions between the fingers and LF domains were suggested to be responsible for promoting G mismatches with T [42]. Finally, detailed analysis of the crystal structure of the Polι catalytic domain reveals that unlike other Y-family members, Polι binds template bases in a *syn* conformation. This induces formation of Hoogsteen, rather than Watson-Crick base pairing with the incoming nucleotide and explains the high fidelity and efficiency of Polι opposite template A and low fidelity and efficiency opposite template T [52]. Additionally, Hoogsteen base-pairing provides Polι with the ability to incorporate nucleotides opposite certain DNA lesions [53]. Interestingly, based on crystallographic analysis, it appears that upon dNTP binding, Polι does not undergo a conformational change, but instead, its active site and the incoming nucleotide, cause template A and G bases to convert from the *anti* to *syn* conformation. This is in contrast to replicative polymerases that undergo conformational changes upon dNTP binding [40]. Interestingly, contradictory evidence indicates the presence of wobble base pairing rather than Hoogsteen pairing [54]. Alternatively, it has been suggested that depending on local conditions, Polι may utilize strategies including Watson-Crick, Hoogsteen, or other possible base pairing mechanisms to bypass bulky lesions [55].

Based on evolutionary analysis of Polι sequences from various organisms, Makarova et al. hypothesized that the substitution of L62 to isoleucine is responsible for decreases in Polι accuracy [24]. In addition, further analysis of Polι sequences indicates that Y39A and Q59A substitutions significantly reduce the catalytic activity of Polι, but increase its fidelity [56].

Another factor that considerably influences the enzymatic properties of Polι is the type of divalent cation for catalysis activation. *In vitro* experiments demonstrate that Polι can synthesize DNA using $Mg^{2+}$, the most abundant divalent cation and general replicative polymerase cofactor, but does so at a much narrower concentration range of 50-250 μM compared to other polymerases [57]. Interestingly, unique among Y-family polymerases, Polι exhibits a strong preference for $Mn^{2+}$ over $Mg^{2+}$ as a catalytic activator and has an optimal $Mn^{2+}$ concentration of 75 μM [57]. Such preference is supported by structural and pre-steady-state kinetic studies, which show that $Mn^{2+}$ causes 2-3 times more efficient Polι catalysis compared to $Mg^{2+}$ [58]. Additionally, cell extracts from various mouse organs all show Polι activity when $Mn^{2+}$ is the cofactor while using $Mg^{2+}$ only triggered Polι activity in testes and brain cell extracts [59]. $Mn^{2+}$ use also reduces the fidelity of Polι opposite template A but increases its fidelity by 3-5-fold opposite template T. Additionally, $Mn^{2+}$ helps stimulate lesion bypass by Polι [57]. However, Polι activity is efficiently inhibited by the divalent cations $Cd^{2+}$ and $Zn^{2+}$ [60].

Polι shows relatively low processivity, and in general, can incorporate only 2-3 nucleotides once bound [2]. However, *in vitro* analysis using different DNA substrates shows that Polι robustly fills 1-nt gaps and performs limited strand displacement, although Polι was unable to initiate synthesis with a nick-containing template [61]. Additionally, incorporation of nucleotides by Polι at the end of DNA is template-dependent and is highly error-prone. Polι can also extend single and tandem mispairs, and is especially efficient in extending tandem mispairs that occur within a short gap [61]. Polι is able to extend all 12 types of mispairs, but the efficiency of this extension depends on both the sequence at the 3′ end of the primer and the template context. In general, extensions from matched and mismatched pairs are most efficient and accurate when A is the next template base and are least efficient and accurate when T is the next template base. Zhang et al. observed that Polι, when opposite template T frequently aborts DNA synthesis in a so-called “T stop” [3]. One exception to this rule is the extension of a G:T mispair, which is more often correctly extended when T is in the template, thus fixing mutations in a TT template [62].

In addition to its polymerase activity, Polι also exhibits intrinsic 5’-deoxyribose (dRP) lyase activity that catalyzes excision of 5’-dRP groups from DNA during base excision repair (BER) [63]. The Polι dRP lyase domain maps to the N-terminal catalytic domain between 79-445 aa [43]. The dRP lyase activity of Polι is estimated to be ~30-fold lower than that of Polβ, the best known BER polymerase, however, the ratio of dRP lyase to polymerase activity in Polι is much higher than for Polβ [43]. Participation of Polι in BER using its dRP lyase and polymerase enzymatic activities has been confirmed using *in vitro* reconstitution reactions involving purified uracil-DNA glycosylase, apurinic/apyrimidinic (AP) endonuclease, DNA ligase I, and Polι to repair G·U and A·U mispairs in DNA, with similar average error rates observed for Polι and Polβ [63]. Additionally, in the *in vitro* single-nucleotide BER Polι has complemented deficiency of Polβ [43] and BER activity was reduced in extracts from cells downregulating Polι [64]. In contrast, Haracska et al. proposed that binding of Polι and other Y-family polymerases to 5′-dRP groups acts as a covalent trap of these polymerases, thus excluding their participation in DNA synthesis during BER [65]. Interestingly, Polι cannot fully complement Polβ deficiencies *in vivo*, as Polβ-deficient mice are not viable [66].

## 6. DNA lesions bypassed by Polι

The ability of Polι to synthesize DNA using substrates containing variety of lesions has been extensively examined *in vitro*. While Polι can incorporate deoxynucleotides opposite many lesions, it is generally unable to extend resulting products, thus the bypass of these lesions often requires the combined action of Polι and Polζ, Polκ, or Polθ [4,22,67–69].

Abasic (apurinic/apyrimidinic, or AP) sites are frequently occurring and highly mutagenic DNA lesions that can form spontaneously or as intermediates of BER. Replicative DNA polymerases can inefficiently bypass these lesions, preferentially inserting A opposite them. In contrast, Polι does not follow this “A-rule” and efficiently incorporates 1 nt, typically either a G or T, in a unique mechanism [3,4,70–72] that is significantly stimulated by the presence of $Mn^{2+}$ [57].

UV-irradiation induces a variety of potentially mutagenic DNA lesions of which cis-syn cyclobutane pyrimidine dimers (CPDs) and 6-4 pyrimidine photoproducts (6-4PPs) are the most abundant. CPD, the most common UV lesion, is efficiently and accurately bypassed by Polη, while conflicting data exist regarding CPD bypass by Polι. In contrast to

Polη, *in vitro* experiments indicate that Polι generally has difficulty bypassing CPDs [4,70]. However, extended incubation times and excess amounts of enzyme allow for insertion of 1 or 2 nucleotides opposite the lesion by Polι, with misincorporation rates 150-300-fold higher than that for Polη [73]. Additionally, a stimulatory effect on Polι by $Mn^{2+}$ of almost 25-fold in bypassing CPDs has been reported [57]. The second most frequent UV lesion, 6-4PP is less problematic for Polι despite its structurally distorting effects. Opposite a 3′T of this lesion, Polι efficiently inserts all four types of nucleotides, with a preference for correct A residues [4,73]. Opposite a 5′T, Polι preferably inserts G, especially if A was incorporated opposite the 3′T [73]. However, Polι cannot extend past a 6-4PP lesion, and TLS is completed in cooperation with Polζ [4,73]. Interestingly, it seems that the sequence context of both UV lesions has a strong impact on the efficiency of their bypass by Polι [22,74].

Polι is also able to bypass one of the most abundant and mutagenic oxidative lesions in DNA, 8-oxoguanine (8-oxoG). In fact, Polι exhibits the highest fidelity among all Y-family polymerases when bypassing 8-oxoG, as it predominantly incorporates correct C or, to a lesser extent, G. However, the efficiency of an 8-oxoG bypass is lower than Polι efficiency opposite undamaged G and lower than for other Y family polymerases and Polβ [70,75–76]. Crystal structure analysis has revealed that the preferable incorporation of correct C opposite 8-oxoG lesions is a consequence of Hoogsteen bonding [77]. Additionally, PCNA stimulates C incorporation opposite 8-oxoG lesions [78]. While bypassing the oxidative lesions 5-hydroxycytosine and 5-hydroxyuracil, both stable products of cytosine oxidation, Polι preferentially incorporates a correct G opposite 5-hydroxycytosine and an incorrect T opposite 5-hydroxyuracil [75].

Uracil can be mistakenly incorporated into DNA or generated from cytosine deamination and is a common DNA lesion estimated to occur at a rate 70-200 events per day per cell [79]. It is normally faithfully repaired by BER, however, when uracil generation escapes repair and remains in DNA, it is highly mutagenic. Uracil is a non-blocking lesion and can be bypassed by most polymerases through incorporation of A opposite U. When uracil is generated by cytosine deamination, this incorporation thus results in a C→T transition [80]. Polι, however, incorporates G and T opposite U more efficiently than A. T misincorporation results in poor extension while G incorporation allow for efficient extension, consequently providing error-free bypass of uracil derived from deaminated cytosine [75]. Alternatively, the inaccurate incorporation of G opposite T by Polι may be beneficial for genome stability maintenance when T is a product of 5-methyl-cytosine deamination [81].

Alkylating agents, which are common reactive chemicals of environmental and cellular origin, can generate a variety of DNA lesions by alkylating ring nitrogens and extracyclic oxygen in DNA bases. The lesion 1-methyl-adenine is highly cytotoxic and forms in DNA through reactions with $S_N2$ methylating agents like methyl methanesulfonate (MMS). This methylation hampers formation of Watson-Crick pairs and strongly blocks replicases. Both Polι and Polη can faithfully bypass these lesions, resulting in 1% mutation rates, although Polι requires the action of Polθ to extend DNA synthesis after incorporation of a nucleotide opposite the lesion by Polι [69]. Steady state kinetic and structural studies show that Polι most efficiently incorporates a T opposite this lesion [82].

Another DNA lesion commonly formed upon treatment with many methylating agents is 3-methyl-adenine, which obstructs replicase interaction with the minor groove of DNA. Polι, similar to Polη, incorporates T opposite 3-methyl-adenine, although this incorporation occurs with reduced efficiency compared to that opposite undamaged template A and the strand cannot be efficiently extended by Polι [83–84]. Opposite 3-methyl-cytosine, Polι preferentially misincorporates T [85]. In addition, Polι can introduce nucleotides opposite the poorly repairable lesions $O^2$-alkyl-thymidines and $O^4$-alkyl-thymidines but cannot extend beyond them [86–87]. $O^6$-methyl-guanine is one of the most mutagenic lesions induced by DNA-alkylating agents, including endogenous compounds. Polι shows a strong preference for T incorporation opposite this lesion (10-fold higher than C) [88] due to Hoogsteen bonding, as revealed by crystal structure analysis [89]. Similarly, opposite the $O^6$-adduct $O^6$-carboxymethylguanine, Polι preferentially incorporates T, but is ineffective in extending the resulting mismatch [90].

Despite the fact that many polymerases contain a single residue in their active sites that functions as a steric gate to prevent the incorporation of NTPs into DNA, ribonucleotides can be incorporated into DNA and are common lesions. For Polι, Y39 functions as a steric gate and is conserved throughout the Y family of polymerases [91]. Interestingly, the Y39A mutation, while reducing sugar discrimination, increases base selectivity. The efficiency of NTP incorporation by wild type Polι is about 1000 times lower than for dNTPs and extension after NTP incorporation is only efficient in the presence of accessible dNTPs. Additionally, in contrast to its paralogue, Polη, Polι can also place ribonucleotides opposite DNA lesions like abasic sites or 8-oxoG [91].

Polι also has the ability to incorporate nucleotides opposite bulky DNA lesions, like 2-acetylaminofluorene (AAF) adducts, that block many other polymerases. Opposite AAF-adducted G, Polι accurately inserts C [70].

Diol epoxides, such as benzo[*a*]pyrene diol epoxides (BPDEs), are polycyclic aromatic hydrocarbon metabolites present as common, highly mutagenic, and carcinogenic environmental pollutants. Bulky adducts like dG-BPDE and dA-BPDE are not efficiently bypassed by Polι, even when acting in combination with Polζ [92]. However, within a variety of sequence contexts, dA-BPDE can be efficiently bypassed through Polι incorporation of T followed by elongation by Polκ [93]. Similarly, Polκ assists in replication past 4-hydroxyequilenin after incorporation of T by Polι opposite the lesion [94].

The minor groove atom $N^2$ of G is highly reactive and can conjugate with different sizes and types of adducts, including those induced by potential carcinogens [13]. It has been proposed that Polι is able to synthesize DNA using templates containing minor groove adducts due to its unique Hoogsteen base-pairing ability followed by extension of nascent DNA by Polκ [39,95–98]. However, Polι also appears capable of performing extension after initial incorporation of C opposite $N^2$-ethylguanine [99]. The catalytic efficiency of Polι in bypassing minor groove adducts depends on adduct hydrophobicity and bulkiness [100]. Primer extension assays and shuttle vector technology demonstrated that Polι preferentially inserts C opposite to $N^2$-substituted-guanine lesions, confirming its accuracy and efficiency in bypassing minor groove $N^2$-guanine adducts [101,102].

The results of *in vitro* TLS experiments have shown that Polι is also able to incorporate nucleotides opposite several other DNA lesions, including 1,$N^2$-etheno(ε)guanine (incorporates T and C) [103], 1,N-ethenodeoxynosine [104], heptanone-etheno-cytosine (incorporates T) [105], 3-(20-deoxy-β-D-erythro-pentofuranosyl)pyrimido-[1,2-a]purin-10(3 H)-one (incorporates C) [106], N(oxypropenyl)-2'-deoxyadenosine (incorporates T and C) [107], and 8,5'-cyclo-2'deoxyadenosine and 8,5'-cyclo-2'-deoxyguanosine tandem lesions [108]. Polι can also bypass N-deozyguanosin-8-yl-1-aminopyrene resulting from reaction with the mutagen and the potential carcinogen 1-nitropyrene; however, based on its efficiency and fidelity, it is not the polymerase of choice [109–110]. Interestingly, Polι can process DNA duplexes with breaks of different sizes and clustered DNA lesions containing AP sites and 5-formyl-uracil [111].

The repair of intra- and intercrosslinks (ICLs) induced by many cancer therapeutics like cisplatin and mitomycin C requires the coordinated action of various repair mechanisms and TLS [112]. Polι does not appear to be the main TLS polymerase involved in ICL repair and contradicting results have been obtained regarding its ability to bypass cisplatin-triggered major groove intrastrand guanine adducts [113–115]. However, Polι faithfully incorporates C opposite acrolein-mediated minor groove ICLs [116] and, through sequential action with

**Table 1**
Major DNA lesions bypassed by Polι

| DNA lesion | Preferred nucleotide | Reference |
|---|---|---|
| Abasic site | G | [4,70,72] |
| 6-4PP | | [4,73] |
| 3′T | A | |
| 5′T | G | |
| 8-oxoG | C | [70,75] |
| U | G | [75] |
| G-AAF | C | [70] |
| 1-methyl-A | T | [69] |
| 3-methyl-A | T | [83,84] |
| 3-methyl-C | T | [85] |
| $O^6$-methyl-G | T | [88] |

Polκ, promotes the bypass of psoralen-induced ICL [117]. Moreover, participation of Polι and other polymerases in bypassing DNA-peptide cross-links has been shown [118].

A brief summary of the major DNA lesions bypassed by Polι and the nucleotide preferably incorporated opposite each particular lesion is presented in Table 1. A detailed summary and verification of Polι *in vitro* translesion synthesis with sequence context consideration is presented by Vaisman et al. [22]. Additionally, it is worth noting that the published results on Polι bypass of various substrates often differs between groups due to differences in reaction conditions, such as variations in salt concentration or divalent cation choice for *in vitro* reactions.

Compared to the elaborate *in vitro* analysis of Polι incorporation of nucleotides opposite a variety of DNA lesions, much less is known about Polι participation in DNA lesion bypass *in vivo* and available results are often inconsistent due differences in cellular backgrounds, systems, and conditions. In addition, it must be remembered that contradictory results exist regarding Polι activity in cells from 129-derived mouse strains, which are frequently used as models for investigating the physiological functions of Polι [119–121]. Analysis of mice carrying defective Polι showed unchanged mutagenesis levels and mutational spectra compared to the wild type mice [122]. Moreover, Okhumo et al. reported that a lack of Polι protein has no effect on the UV sensitivity of murine fibroblasts, even in a Polη-deficient background [32], while Dumstorf et al. noticed a small but statistically significant increase in the UV-sensitivity of mouse primary fibroblasts lacking Polι, regardless of the presence of Polη [123]. Gueranger et al. reported enhanced UV sensitivity in type I Burkitt's lymphoma BL2 cell lines deprived of both Polη and Polι compared to the $POLH^{-/-}$ clone; yet, $POLI^{-/-}$ UV sensitivity was similar to that of wild type cells [124]. Similar results were also observed for human fibroblasts with Polι downregulation [64] and for Polι-deficient mouse embryonic fibroblasts (MEFs) [125]. Jansen et al. compared the UV sensitivity of MEFs deficient in Polη, Polι, or Polκ, or with a combination of double and triple deficiencies and suggested that Polι only functions to a minor extent as a backup for Polη in bypassing photolesions [126].

Differing results have also been described regarding UV-induced mutagenesis. Analysis of mutational spectra in *supF* and *lacZ'* genes in Polι-deficient cells suggests that Polι does not play a significant role in UV lesion bypass and UV-induced mutagenesis [124,127]. However, several other lines of evidence imply engagement of Polι in TLS past UV lesions in mammalian cells. First, Dumstorf et al. observed suppression of increases in UV-induced mutagenesis due to Polι inactivation at the endogenous *Hprt* locus regardless of Polη activity, suggesting participation of Polι in the mutagenic bypass of UV photoproducts [123]. Similarly, error-prone participation of Polι in TLS past UV lesions in the absence of Polη is suggested by results from the study by Kanao et al., who observed alleviation of UV-induced mutation frequency in Polη/Polι deficient mice compared to Polη-deficient mice [128]. Moreover, mutation levels in XPV cells devoid of Polη tightly correlate with the levels of Polι expression [129]. In addition, despite the fact that Polι inactivation alone does not promote skin tumor development, Polι protein may function to suppress UV-induced tumor development in Polη-deficient backgrounds. UV-induced skin tumors in Polη- and Polι-deficient mice developed 4 weeks earlier than in mice lacking only Polη and a lack of Polι stimulates UV-induced mesenchymal carcinogenesis [123,32]. In summary, most studies, even those using different strategies, indicate a role for Polι in the bypass of UV-induced lesions, especially in the absence of Polη.

The expression of human Polι in yeast mutants that are highly sensitive to alkylating agents, like *Δmag1 Δrad30* and *Δmag1 Δrad30 Δrev3*, displayed enhanced resistance to MMS, suggesting that Polι can replicate DNA past 3-methyl-adenine lesions [130,83]. However, a lack of Polι in Polβ-deficient mouse fibroblast cells hardly had any effect on MMS sensitivity, compared to cells only deficient in Polβ [131]. Additionally, human fibroblast cell lines showing Polι downregulation and wild-type cells show similar sensitivities to ethyl methanesulfonate (EMS) [64]. Nonetheless, embryonic fibroblasts derived from Polι knock-out mice show three times higher sensitivity to MMS compared to wild-type cells [132]. Moreover, Yoon et al. showed that in human cells, TLS opposite 3-methyl-adenine seems to occur in a highly error-free manner compared to TLS *in vitro* experiments and, in one of the pathways involved, Polι functions with Polκ to perform TLS [84]. Many alkylating agents also react with $N^2$ of guanine to form an array of $N^2$-alkyl-lesions like $N^2$-methyl-guanine, $N^2$-ethyl-guanine, and $N^2$-propyl-guanine, which can be bypassed by Polι either alone or with Polκ or Polζ [133].

Interestingly, in human fibroblasts with significantly reduced Polι expression mediated by RNA interference, increased sensitivity to oxidative stress caused by hydrogen peroxide or menadione was not affected by Polβ downregulation, but could be reversed by ectopic expression of Polι. Moreover, exposure of Polι-deficient cells to oxidants caused problems with S phase entrance, causing accumulation of G1 phase cells [64]. In addition, increased sensitivity to the oxidative agent potassium bromide has been shown in human embryonic fibroblasts lacking Polι [132]. Furthermore, 4-hydroxynonenal, generated by polyunsaturated fatty acid peroxidation and endogenous stress, strongly sensitizes Polι-deficient MEFs, suggesting that Polι is important for the efficient bypass of 4-hydroxynonenal-induced lesions [134].

## 7. Regulation of Polι levels and activity

Sabbioneda et al. estimated that only a small fraction of Polι is engaged in TLS at the same time [135]. During the G2-M-G1 phases of the cell cycle, Polι is equally distributed throughout the nucleus; however, during the S phase, it localizes to microscopically visible subnuclear replication foci where replication-associated factors are concentrated [25]. However, TLS polymerases can also be recruited to replication factories without the formation of observable foci, and formation of foci does not guarantee that a protein is permanently bound to DNA [124]. Similar to Polη, Polι transiently binds DNA for a duration of 100-200 ms. The mobility of Polη and Polι is slightly reduced in replication foci and formation of Polι foci seems to depend significantly, but not entirely, on the presence of Polη [135,25]. UV radiation, but not MMS treatment or γ-irradiation, stimulates Polι foci accumulation; however, UV-dependent Polι foci induction is not associated with increased Polι expression [25].

In various types of tissues, Polι is generally expressed at low or medium levels and DNA damage-induced expression of Polι is not observed in normal cells. In contrast, there have been several reports describing transcriptional regulation of Polι in cancer cells. Significant increases in Polι expression occur in cancer cells during hypoxia [136]. In contrast to other TLS polymerases such as Polη, Polκ, and Polμ, induction of Polι transcription is dependent on the hypoxia-inducible

factor HIF-1α. HIF-1α, together with the constitutively expressed HIF-1β subunit, form the heterodimer HIF-1, a master player in an adaptive strategy to hypoxia that enhances the expression of *POLI* gene by binding the hypoxia response element (HRE) site at +330 bases in intron 1 of *POLI* [136]. Moreover, analysis of the *POLI* promoter revealed a *cis*-acting element between -1631 and -794 and the Sp1 transcription factor was shown to bind between -1291 and -1081, resulting in four-fold increased *POLI* expression in esophageal cancer tissues compared to normal tissues [35]. Furthermore, Yuan *et al*. localized a putative AP-1 binding *cis*-element within a minimal promoter (-275/+63) at the -228 site and showed that c-Jun, which plays a central role in AP-1 complex function, can activate transcription of *POLI* gene using this AP-1 *cis*-element [137]. Interestingly, the c-Jun-dependent dysregulation of *POLI* expression is also observable in bladder cancer cells [137].

Despite the presence of CpG islands near the transcription start site of *POLI*, which suggests that *POLI* transcriptional regulation potentially occurs through DNA methylation, analysis of increased *POLI* expression in esophageal cancer tissues indicates that epigenetic regulation is not likely to be involved in *POLI* transcription regulation [35].

Unexpectedly, the activity of Polι and other Y family polymerases, but not A, B, or X family polymerases, is stimulated by the biologically active sphingolipids sphingosine and dihydrosphingosine, which play roles in controlling cell proliferation via cell signaling [138].

## 8. Interacting partners and their influence on Polι function

The C-terminal half of Polι is rich in protein-protein interaction domains that regulate the recruitment of Polι to the replication fork and influence its function. However, it seems more likely that Polι transiently interacts with its binding partners rather than forming stable complexes. Similar to other Y-family polymerases, Polι physically interacts with PCNA, which acts with replication factor (RFC) and replication protein (RPA) to stimulate Polι polymerase activity, although this does not affect Polι fidelity [139]. Polι interacts with PCNA through the single PIP box located in the center of Polι immediately downstream of the LF domain. Similar to other PCNA-interacting proteins, such as Polδ or p21, Polι binds PCNA at the PCNA interdomain connector loop (IDCL) [46–47]. It appears that the interaction of Polι and PCNA stimulates DNA synthesis by Polι in a PIP-dependent manner and controls localization of Polι to cellular replication machinery and accumulation at sites of DNA damage [46]. The interaction through the PIP box of Polι, is rather weak, as it is for other Y-family polymerases, and PCNA-Polι interaction can be significantly strengthened through PCNA monoubiquitination, which forms an additional surface for interaction. All four Y-family polymerases have one or two ubiquitin binding domains that non-covalently bind ubiquitin and ubiquitinated proteins like monoubiquitinated PCNA. Polι has two functional ubiquitin binding motifs, UBM1 and UBM2, and the accumulation of Polι in replication foci depends on its ability to bind ubiquitin [49–50]. Both UBMs are required for proper recruitment of Polι to replication foci [140] and the conserved UBM motif containing leucine and proline plays an important role in ubiquitin binding. Interestingly, while most known UBDs require the presence of conserved I44 in the hydrophobic patch of ubiquitin for binding, Polι instead requires L8 in ubiquitin [49,141]. Additionally, Polι can interact both with monoubiquitin and K63-linked polyubiquitin chains while contradictory results have been reported regarding binding of K48-linked ubiquitin chains [50,142]. Moreover, in contrast to Polη and Polκ, Polι does not promote the monoubiquitination of PCNA [143].

Polι is known to interact physically and functionally with the Y family polymerases Rev1 and Polη. Rev1 forms a scaffold for other TLS polymerases at stalled replication forks and assists in polymerase switching [11] through interaction of its approximately 100 amino acid C-terminal domain (CTD) with special domains located in the other polymerases [144–145]. Polι, Polη, and Polκ have short RIRs containing two consecutive, centrally located, conserved phenylalanine residues critical for interaction with Rev1-CTD [48]. The significance of another RIR helix residue highly conserved in vertebrates, K550, is uncertain due to inconsistent results [146–147]. Interaction of Rev1 with Polι appears to be much weaker than with Polη or Polκ [148] and the requirement of Rev1 for subcellular localization of Polι and other Y-family polymerases in response to DNA damage is disputable [46,149].

Based on results of co-localization studies, yeast two hybrid assays, and *in vitro* experiments, Kannouche et al. suggest that Polι directly interacts with Polη and that the last 224 amino acids of Polι and the last 119 amino acids of Polη (595-713 aa), which contain a nuclear localization signal, ubiquitin-binding domain (UBZ), and a PCNA-interacting peptide, are sufficient for this association [25]. Later experiments confirmed that the UBZ and UBMs of both polymerases are required for Polη and Polι interaction, however, the polymerases do not associate directly through their UBDs and, but interact in a ubiquitin-mediated manner [150]. Due to the potential for ubiquitination of both polymerases, the physical interaction between them can occur *via* the ubiquitinated form of either polymerase and the UBD of the interaction partner [150]. In response to DNA damage, the localization of both polymerases in replication foci is identical and in XPV cells lacking Polη, the number of UV-induced Polι foci drops several times. It was therefore proposed that Polη is involved in recruiting Polι to replication machinery stalled at DNA damage sites [25]. However, analysis of replication foci kinetics of both polymerases suggests that Polι dissociates from replication foci more rapidly than Polη and that interactions between the two polymerases are rather transient or unstable [135]. Additionally, Petta et al. showed that Polι localization after laser-irradiation, which produces single- and double strand breaks and base damage, was unaltered in XPV cells, suggesting that Polη is not required for Polι accumulation at the site of DNA lesions [64].

Polι also associates with several other proteins, including XRCC1, p53, and p300 during different processes [64,151–152]. DNA repair protein XRCC1 is a molecular scaffold protein that interacts with many proteins involved in BER. Polι associates with XRCC1 and is recruited with XRCC1 and another BER enzyme, Flap Endonuclease 1 (FEN1), to chromatin in response to hydrogen peroxide treatment in human cells [64].

Polι also physically and functionally interacts with p53, the tumor suppressor that, in addition to its role in transcriptional regulation, possesses intrinsic 3′→5′ exonuclease activity. The p53/Polι complex is proposed to transiently stabilize lesion-blocked replication forks by idling, which may lead to either a successful DNA damage bypass or stimulate recombination events [151].

p300 is an acetyltransferase responsible for acetylation of histones and hundreds of non-histone proteins. Additionally, it possesses a non-canonical but functional RING domain characteristic of ubiquitin ligases. Besides acetylating and ubiquitinating proteins, p300 influences multiple cellular processes through interactions with over 400 proteins. Polι interacts with p300 and can also be acetylated by this enzyme. The N-terminal region of Polι, containing its catalytic domain, interacts with p300 in a manner that seems to require the acetyltransferase HAT domain but not the RING domain of p300 [152].

## 9. Posttranslational modifications of Polι

Posttranslational modifications play a pivotal role in the regulation of TLS proteins. Polι is known to be monoubiquitinated, polyubiquitinated, and acetylated [49,152–153]. Monoubiquitination seems to be a common Polι modification, as it has been estimated that up to 20% of Polι is modified by attachment of a single ubiquitin to one of its lysine residues under normal conditions [153]. In contrast to PCNA and Polη, Polι does not seem to have a major ubiquitination site or even a ubiquitination-dedicated region. Instead, mass spectrometry analysis revealed 27 potential unique ubiquitination sites located in different functional domains of Polι, and mutation of K715 appears to yield the

greatest reduction in Polι monoubiquitnation [14,153]. However, possession of multiple possible ubiquitination sites does not mean that Polι can be multi-monoubiquitinated, as it appears that monoubiquitinated Polι cannot interact with free ubiquitin or other ubiquitinated proteins [49,150]. So far, the only documented function of Polι monoubiquitination is to facilitate its interaction with Polη [150].

In contrast to Polη, the monoubiquitination status of Polι does not change in response to DNA damaging agents or general replication blocks. However, exposure of cells to menadione and other structurally related 1,4-naphthoquinones that inhibit p300 acetyltransferases, as well as other structurally-unrelated p300 inhibitors, induces rapid Polι polyubiquitination via attachment of K11- and K48-linked polyubiquitin chains [153]. Furthermore, Polι can be directly acetylated by p300/CBP acetyltransferases. Despite the fact that K550, located in the RIR domain, has been identified as the main acetylation site, this acetylation does not seem to interfere with interaction of Polι and Rev1. Interestingly, acetylation of Polι is significantly induced by alkylating (particularly $S_N2$ type) and oxidative agents. Importantly, this acetylation seems to be specific for Polι, as its closest paralogue, Polη, is not acetylated under similar conditions [152].

## 10. Possible cellular roles of Polι

The ability to incorporate nucleotides opposite a variety of lesions is the most well recognized role of Polι in DNA damage tolerance during replication. However, there is also evidence that Polι may process lesions in non-S phase cells. Sertic et al. demonstrated participation of Polι and other Y-family polymerases in processing of UV-induced closely-spaced opposing lesions. Polymerases were recruited to sites of local, NER-positive UV damage and Polι and Polκ accumulated at sites only when the nuclease EXO1 was present. It has been suggested that those Y-family polymerases partially help prevent unscheduled DNA synthesis and double-strand breaks [154].

Moreover, because of its infidelity and specific misincorporation pattern, it has often been suggested that Polι may play a role in somatic hypermutation (SHM) of immunoglobulin genes, a process involved in generating antibody variation and in which Polι's error-prone activity would be an advantage [113,155]. Polι, Polκ, Polζ, and Rev1 mRNA is present in normal human B cells and in Burkitt's lymphoma BL2 cell line containing an inducible IgV(H) gene. Out of all of these polymerases, however, Polι showed the highest level of expression (4-fold increase), within 12 h of induction, implying that Polι may be one of main polymerases responsible for SHM [156]. Additionally, fewer mutations were observed in the BL2 line lacking the *POLI* gene compared to the line with restored Polι, suggesting the dependence of SHM on Polι [157]. However, an analysis of mutations in variable genes in Polι-deficient mice indicates no differences in the frequency and spectrum of mutations compared to wild type mice, suggesting that Polι does not participate in SHM or that its role is nonessential and can be performed by another polymerase [158–161]. In addition, Ratnam et al. suggested that Polι may play a role in SHM in cells lacking p53 [162]. Maul et al., based on tandem mutation analysis, proposed a model in which Polι occasionally accesses the replication fork and introduces erroneously one nucleotide, with mismatch extension occurring through a second mutation generated by Polζ [122].

## 11. Misregulation, genomic instability, and cancer

Genome instability is a common feature of tumor cells. Numerous lines of evidence indicate that the function and regulation of Polι differs between cancerous cells and normal cells, implying that Polι is highly regulated in normal cells but once it escapes from this precise regulation, can be a potential mutator. This was first suggested based on results linking Polι misregulation with the hypermutation status of breast cancer cells [33]. Polι expression is increased at both the RNA and protein levels in malignant breast cancer cell lines compared to non-malignant tissues and this elevated expression correlates with enhanced DNA replication infidelity. Interestingly, in response to UV treatment, Polι expression in breast cell lines, particularly in malignant cell lines, was 2-7 times higher within 0.5-2 hours after treatment, suggesting the existence of an early response to UV-mediated DNA damage. In addition, the enhanced level of UV-induced mutations, which consisted of point mutations in > 90% of cases, is Polι-dependent [33]. Polι upregulation has also been observed in a number of glioma specimens and its levels are correlated with poor clinical outcomes [163]. Moreover, in cells from high-grade invasive bladder tumors, elevations in Polι level are dependent on the activated JNK/c-Jun pathway and are associated with increased mutation frequency [137]. In contrast, the analysis of over one hundred paired specimens of cancerous and non-malignant samples revealed the downregulation of Polι, Polκ, Polζ and, in many cases, Polη in human lung, stomach, and colorectal cancers [34]. Additionally, defects in Polι are linked to increased susceptibility to urethane or diethylnitrosamine-induced lung tumors [31,164]. Interestingly, the examination of Polι expression levels in 68 clinical cancer specimens from kidney, breast, prostate, uterus, cervix, colon, lung, stomach, or rectums compared to matched adjacent normal tissues revealed over two-fold overexpression in 29% of tumor samples and less than 0.5-fold reductions in expression in 20% of tumor samples [30]. These results thus indicate that both the upregulation and downregulation of Polι can be correlated with different types of cancer, underlining the necessity of the strict control of Polι protein levels.

Analysis of 24 normal esophageal tissue samples and 60 esophageal squamous cell carcinoma (ESCC) samples revealed significantly higher levels of *POLI* mRNA (over 7-fold upregulation) in carcinoma tissues compared to normal tissue [35]. Further analysis showed that esophageal cancer cells overexpressing Polι are more invasive and in general presented more aggressive phenotype coupled with poorer prognoses [36,165]. In addition, invasion and metastasis of ESCC cells is activated by Polι-dependent phosphorylation of Erk1/2, which in turn induces phosphorylation of Y38 in the proto-oncogene ETS1/2, a key regulator of cancer progression [166]. Similarly, results of studies of lung and breast cancer cells also suggested a role of Polι in promoting cell migration and invasion via influence on expression of E- and N-cadherin as well as MMP2 and MMP9, which are all proteins associated with tumor cellular adhesion, motility, and other invasive properties [167,168]. Additionally, enhanced expression of the *POLI* gene has also been observed in some XPV tumor cells [169].

There is no known disorder resulting from Polι deficiencies, however, several Polι SNPs are correlated with certain cancers. I236M, located in the thumb domain and affecting fluctuations in expression levels, is linked to melanoma [170]. Furthermore, F507S, located in UBM1, correlates with prostate cancer occurrence [171] while T706A, located in UBM2, is associated with an increased risk of adenocarcinoma and squamous cell carcinoma in lungs [172].

## 12. Biological consequences

People with altered Polι function, either through changes in expression level or genetic variations, exhibit no obvious health problems despite individual risks of mutations and increased predisposition to cancer via genotoxin exposure. Nonetheless, Polι may influence occurrence of poorer prognoses in the development of many cancers. Additionally, due to its ability to bypass a variety of types of DNA lesions, one can imagine that Polι, similar to Polη and other TLS polymerases, may hamper the effectiveness of anticancer therapies based on introducing DNA damage or nucleoside analogs to actively dividing tumor cells [112,173–174]. In addition, the pro-mutagenic effects of Polι and other Y family polymerases may cause acquisition of drug-induced mutations related to treatment resistance by tumors, increased risks of secondary malignancies, and cancer relapse. Additionally, the activity of Polι and other non-canonical human polymerases also appears responsible for unwanted side effects and drug toxicity of

nucleoside reverse transcriptase inhibitors used in antiviral therapy against HIV and hepatitis B [175–176]. Consequently, TLS polymerases are promising new targets of improved cancer therapies or supplementary therapies aiming to reduce chemotherapeutic resistance in various tumors and unwanted cytotoxicity [177]. The unique properties of TLS polymerases, including distinctive base pairing by Polι, increases the chance of generating small molecule modulators specifically targeting particular enzymes [178]. Related drug discovery efforts are still at their early stages; however, some results of investigations into TLS polymerase inhibitors using natural compound and small molecule inhibitor screening and other approaches have been reported [15,178–182].

## Declaration of Competing Interest

The author declares that there are no conflicts of interest.

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