ISSN 0006-2979, Biochemistry (Moscow), 2020, Vol. 85, No. 4, pp. 425-435. © Pleiades Publishing, Ltd., 2020.
Published in Russian in Biokhimiya, 2020, Vol. 85, No. 4, pp. 494-506.

REVIEW

Translesion DNA Synthesis and Carcinogenesis

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Received December 4, 2019
Revised February 20, 2020
Accepted February 20, 2020

Abstract—Tens of thousands of DNA lesions are formed in mammalian cells each day. DNA translesion synthesis is the main mechanism of cell defense against unrepaired DNA lesions. DNA polymerases iota (Pol ι), eta (Pol η), kappa (Pol κ), and zeta (Pol ζ) have active sites that are less stringent toward the DNA template structure and efficiently incorporate nucleotides opposite DNA lesions. However, these polymerases display low accuracy of DNA synthesis and can introduce mutations in genomic DNA. Impaired functioning of these enzymes can lead to an increased risk of cancer.

DOI: 10.1134/S0006297920040033

Keywords: translesion DNA synthesis, DNA damage, mutagenesis, carcinogenesis

Somatic mutations in tumor suppressor genes and oncogenes are one of the main factors triggering carcinogenesis. Mutations are generated by deamination of 5-methylcytosine and cytosine, defects in DNA repair, and replication errors. Failures in the functioning of DNA repair and replication enzymes lead to the accelerated accumulation of somatic mutations [1].

Mutations can originate not only from mistakes in the replication of intact DNA, but also due to the errors caused by spontaneous and induced DNA damage. DNA is constantly exposed to various physical and chemical factors. DNA repair enzymes efficiently remove DNA lesions, restoring the original structure of DNA molecule; however, some of the damaged sites remain unrepaired and can lead to cell death as a result of replication fork block and cell cycle arrest. DNA lesions also exhibit mutagenic properties as many damaged bases form hydrogen bonds with bases that are not complementary to the original intact sequence [2]; some mutagenic lesions simultaneously possess cytotoxic properties (e.g., apurinic/apyrimidinic sites, AP sites).

Translesion DNA synthesis (TLS) is an alternative mechanism that protects cells against DNA damage. The key role in this process in mammals belongs to specialized translesion* DNA polymerases: zeta (Pol ζ) of the B-family and iota (Pol ι), eta (Pol η), kappa (Pol κ), and REV1 of the Y-family [2-5]. Translesion DNA polymerases have an active site that is not stringent toward the DNA template structure, so they can efficiently incorporate nucleotides opposite to lesions, overcoming the replication arrest [5, 6]. In many cases, translesion DNA polymerases incorporate nucleotides complementary to damaged bases. Such synthesis is quite accurate and makes a significant contribution to the reduction of DNA damage-induced mutagenesis.

However, the accuracy of DNA synthesis by translesion DNA polymerases is low because of the high active site tolerance, the absence of proofreading 3′-5′ exonu-

Abbreviations: BER, base excision repair; MMR, mismatch repair; NER, nucleotide excision repair; PCNA, proliferating cell nuclear antigen; SHM, somatic hypermutation; TLS, translesion DNA synthesis.

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* By translesion DNA polymerase, we mean a DNA polymerase, the main cellular function of which is DNA synthesis on damaged DNA, and demonstrating high efficiency of nucleotide incorporation opposite damaged DNA bases *in vitro* and *in vivo*.

clease activity, and possibility of noncanonical interactions during nucleotide incorporation [5, 6]. Such low accuracy would be unacceptable in the replication of undamaged DNA. The activity of error-prone DNA polymerases and their access to the replication fork are tightly regulated; disruption of their functions (e.g., increase/decrease in the catalytic activity, hindered access to the replication fork) can cause accelerated accumulation of mutations and tumorigenesis. In this review, we discuss the main functions of Pol ζ, Pol ι, Pol η, Pol κ, and REV1 and their possible role in the promotion or prevention of carcinogenesis.

FUNCTIONS OF DNA POLYMERASES IN THE CELL

Human DNA polymerases belong to several families. They are highly diverse in their biochemical properties, accuracy of DNA replication, and functions. Replicative DNA polymerases of the B-family, such as polymerases delta (Pol δ), epsilon (Pol ε), and alpha (Pol α), synthesize genomic DNA with a high fidelity, which is achieved by the high selectivity of the active site and the presence of the proofreading 3′-5′ exonuclease activity (in Pol δ and Pol ε) [7, 8]. The error rate during DNA replication by Pol δ and Pol ε (*in vivo* and *in vitro*) is as low as 10^{-5}-10^{-7} errors per base pair [8].

When replicative DNA polymerases encounter DNA damage, a common result is the replication block, which triggers a cascade of events leading to the monoubiquitinylation of PCNA (proliferating cell nuclear antigen) processivity factor at Lys164 and switch to translesion DNA polymerases [5, 9]. Efficient functioning of translesion DNA polymerases requires formation of the translesome – a multisubunit complex consisting of DNA polymerases and regulatory proteins.

According to the two-polymerase model, one of the Y-family DNA polymerases – iota (Pol ι), eta (Pol η), or kappa (Pol κ) – incorporates nucleotides opposite the damaged site, while DNA polymerase zeta (Pol ζ) continues the synthesis beyond the lesion [4]. Pol ι, Pol η, and Pol κ are single-subunit enzymes with a very low accuracy of DNA synthesis on undamaged DNA templates (10^{-1}-10^{-4}) and low processivity [10-12]. These DNA polymerases are "inserters"; their activity is limited to the incorporation of one or few nucleotides opposite the damaged site. Pol ι, Pol η, and Pol κ differ in their biochemical properties, efficiency, accuracy, and the spectrum of nucleotides incorporated opposite the lesions. Despite the fact that translesion DNA polymerases specialize in different types of lesions, their functions partially overlap [2].

Since the Y-family DNA polymerases usually do not catalyze primer extension beyond the DNA lesion, further DNA synthesis (including synthesis from unpaired primer termini) is carried out by Pol ζ, which is an

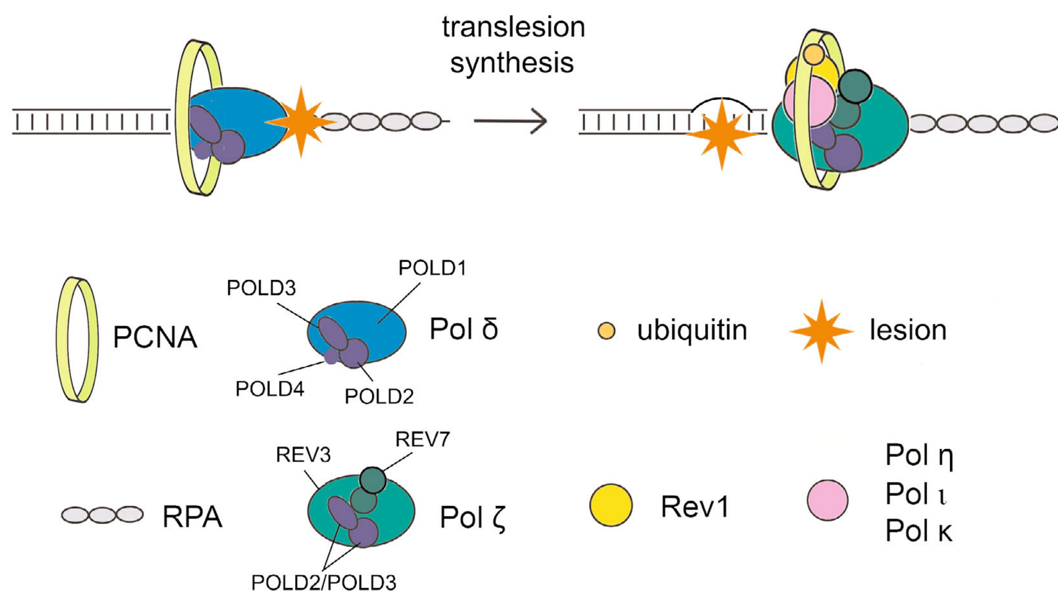

Fig. 1. Translesion DNA synthesis. Translesome assembly and switching of DNA polymerases at the site of DNA damage are initiated by PCNA ubiquitination. Main proteins of the human translesome and protein–protein interactions are shown: (i) POLD2/POLD3 regulatory subunits are shared between Pol δ and Pol ζ, (ii) REV1 simultaneously interacts with ubiquitinated PCNA, REV7 dimer of Pol ζ, and a Y-family DNA polymerase or POLD3 of Pol ζ (the C-terminus of REV1 and the RIR motif of a Y-family DNA polymerase and POLD3), (iii) POLD3 of Pol ζ interacts with PCNA, REV7, and REV1 or a Y-family DNA polymerase. Alternative binding of the REV1 RIR motif by the Y-family DNA polymerase and POLD3 may play a role in the switch between the "inserter" and "extender" polymerases. Interactions between a Y-family DNA polymerase and PCNA [3, 4] are not shown. (Colored versions of Figs. 1 and 2 are available in electronic version of the article on the site http://sciencejournals.ru/journal/biokhsm/)

"extender" DNA polymerase [4]. Pol ζ consists of the catalytic REV3 and regulatory REV7 subunits (in the form of a dimer), POLD2 (p50), and POLD3 (p66) (Fig. 1) [13-16]. The Y-family DNA polymerase REV1 has weak DNA polymerase activity and incorporates dCMP opposite several lesions *in vitro*, but the main function of REV1 is to regulate the activity and coordinate DNA polymerases during translesome assembly [3, 4]. REV1 interacts with Pol ζ, Y-family DNA polymerases, and PCNA processivity factor [3, 4].

Translesion DNA polymerases also perform other functions beside the TLS. Pol κ carries out DNA repair synthesis during nucleotide excision repair (NER) [17]. Pol ι and REV1 possess additional 5′-deoxyribose phosphate (dRP) lyase activity. It was suggested that in some cases, Pol ι and REV1 can replace Pol β in the DNA synthesis during base excision repair (BER) [18, 19]. Pol η and REV1 are involved in somatic hypermutation (SHM) of immunoglobulin genes in B lymphocytes [20-22].

Impaired functioning of translesion DNA polymerases in an organism increases the risk of malignant cell transformation. A decrease in the expression level and disturbances in the functioning of translesion DNA polymerases can be associated with tumor development, while elevated activity of these enzymes in the tumors can be accompanied by chromosomal instability and high mortality of patients due to the increased resistance of cancer cells to chemotherapy.

The correlation between impaired functioning and development of inherited diseases in humans and mice was unambiguously demonstrated for Pol η and Pol ζ [23-25]. Mutations and amino acid polymorphisms in other translesion DNA polymerases have been observed in both healthy people and patients with various types of cancers [see Table S1 in Supplement to this paper on the journal website (http://protein.bio.msu.ru/biokhimiya) and Springer site (Link.springer.com)]. Some polymorphisms were found to be associated with a high risk of developing cancer and negative disease prognosis, which makes them potential cancer prognostic markers.

Massive genome sequencing has revealed the most common mutation patterns (mutational signatures) of tumors [26]. A number of such mutation patterns have been associated with an altered activity or dysfunction of certain DNA polymerases.

Pol η. The main function of Pol η in cells is efficient and accurate replication across photoproducts [cyclobutane thymine–thymine (T-T) dimers] and cell protection from ultraviolet radiation [23]. In addition to the T-T dimers, Pol η efficiently incorporates nucleotides opposite AP sites, 8-oxoguanine (8-oxo-G), thymidine glycol [2], and cisplatin-induced intrastrand crosslinks [14, 27]. The loss of Pol η activity in humans leads to the development of xeroderma pigmentosum variant (XP-V phenotype), an inherited autosomal recessive syndrome characterized by photodermatosis and very high occurrence of skin tumors [23]. In mice, the loss of both *Polη* alleles causes UV-induced skin squamous cell carcinomas in 100% cases, while in the heterozygous animals, the tumors develop in about 30% cases [28].

In patients with the XP-V phenotype, mutations and amino acid polymorphisms in Pol η affect both the catalytic core (catalytically active enzyme containing the active site but lacking the regulatory C-terminal region) and the C-terminal region participating in the protein–protein interactions (Table S2 in the Supplement). On average, mutations in the *POLH* gene increase the likelihood of skin tumor development thousand-fold, and the age of tumor onset is 20-30 years. In most cases, patients simultaneously develop multiple melanomas and basal cell and squamous cell carcinomas of the skin (up to several tens of tumors). Sometimes the disease is accompanied by actinic keratosis and formation of multiple atypical nevi. Isolated cases of eye tumors, trichoblastomas, neurofibromas, keratoacanthomas, and immune defects have been reported (references from Table S2 in the Supplement).

It is assumed that, in addition to its protective function, Pol η contributes to the accumulation of mutations in the genome, leading to carcinogenesis. Pol η is involved in the SHM in the A-T pairs of immunoglobulin genes [21, 22]. Mutational signatures of Pol η have been found not only in B lymphocytes, but also in many types of tumors. Non-targeted mutagenesis of genomic DNA caused by Pol η is believed to be associated with carcinogenesis [29].

Pol ι incorporates nucleotides with a varying accuracy opposite DNA lesions caused by endogenous and exogenous factors, such as AP sites, uracil and its derivatives, 8-oxo-G, N3-me-A, O^6-me-G, and bulky purine adducts that prevent formation of Watson–Crick interactions (e.g., 1,N^6-ethenoadenine and N^2-guanine) [30, 31]. Incorporation of nucleotides opposite the lesions blocking the Watson–Crick interactions occurs via formation of Hoogsteen hydrogen bonds [32, 33]. Pol ι has a very low fidelity in DNA synthesis on undamaged DNA (Fig. 2).

An unusual property of Pol ι is prevalent incorporation of dGMP opposite thymine, uracil, and its derivatives [12, 34, 35]. Incorporation of dGMP opposite T of the template is stabilized by a unique hydrogen bond formed directly between the N^2 atom of dGTP and Gln59 of the Pol ι active site [33, 36]. Also, Pol ι is one of the few DNA polymerases that predominantly incorporate dGMP (and not dAMP) opposite an AP site [2, 30, 35]. These features of the enzyme can play a role in reducing the mutagenic potential of deaminated cytosine, its oxidized derivatives, and 5-methylcytosine (5-me-C) (in the case of AID/APOBEC-induced mutagenesis and spontaneous deamination of 5-me-C in CpG islands) [35]. Deaminated and oxidized cytosine residues account for the majority of pyrimidine lesions in genomic DNA;

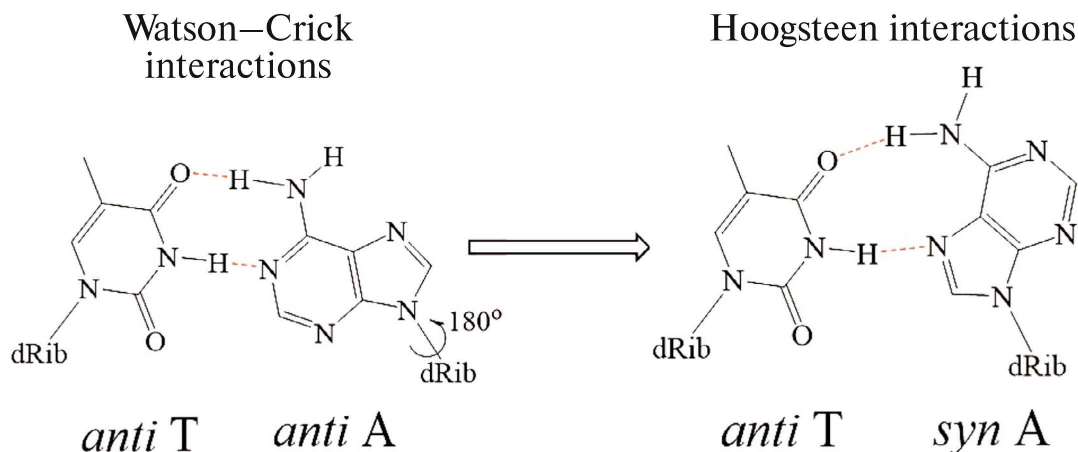

Fig. 2. An example of Hoogsteen base pairs in the active site of Pol ι.

therefore, it can be expected that incorporation of dGMP opposite non-canonical pyrimidines during TLS will be predominantly antimutagenic. However, the role of Pol ι in reducing the mutagenic potential of deaminated cytosine has not been confirmed *in vivo*, and the mechanisms of deaminated cytosine recognition are poorly understood.

A decrease in the expression level and/or activity of Pol ι is associated with the development of oncological diseases. In mice, the *Polι* gene is located in the PAR2 (Mouse Pulmonary Adenoma Resistance 2) locus, which is important in protecting against chemically induced lung cancer [37-39]. The knockout of the *Polι* gene, as well as alternative splicing, mutations, and polymorphisms that reduce the enzyme's activity, are associated with a high risk of developing lung adenomas and adenocarcinomas induced by urethane and diethylnitrosamine [37-39]. The protective effect of Pol ι was also demonstrated for the UV-induced skin tumors (in the absence of Pol ι, mainly mesenchymal skin tumors are formed) [40, 41].

An increased risk of developing lung cancer in humans is associated with the presence in either heterozygous or homozygous state of the *POLI* gene variant (rs8305) encoding the enzyme with the T706A amino acid substitution (Table S1 in the Supplement). An increased risk of prostate cancer is associated with the T706A and F507S substitutions (rs3218786) (Table S1 in the Supplement). A strong association between the formation of the chimeric *TMPRSS2-ERG* gene with the presence of the F507S substitution has been demonstrated in patients with prostate cancer (Table S1 in the Supplement). The fusion of the promoter element of the protease-encoding androgen-regulated *TMPRSS2* gene with the proto-oncogenic transcription factor *ERG* gene can be caused by chromosomal rearrangements and is one of the markers of prostate cancer [42]. The C-terminal Phe507 and Thr706 residues are located in the binding sites for ubiquitinylated PCNA (UBM1 and UBM2, respectively) [43, 44] and can interfere with the Pol ι interaction with the translesome. The I236M substitution in Pol ι can be associated with the melanoma development (Table S1 in the Supplement).

In humans, an increase in the expression and/or activity of Pol ι has been described in brain gliomas [45], esophageal carcinomas [46-48], breast tumors [49], and bladder cancer [50]. High levels of Pol ι expression in esophageal, lung, and breast cancers are associated with a high risk of metastasis and negative prognosis [46, 48, 51-53]. Induction of *POLI* expression is regulated by HIF-1 (hypoxia-inducible factor-1), which stimulates overexpression of *POLI* in tumor cells under hypoxia [54]. The level of *POLI* expression in bladder cancer is regulated by the transcription factor c-Jun and c-Jun-N-terminal kinase and correlates with the disease stage [50].

Pol κ bypasses a wide range of DNA lesions (AP sites, thymidine glycol, 1,N^6-ethenoadenine) with varying efficiency and accuracy. It is accepted that the main targets of Pol κ are nucleotide modifications exposed in the DNA minor groove, primarily large N^2-guanine adducts induced by chemical carcinogens [55-59]. Pol κ reduces the mutagenic potential of the common carcinogen benzo[a]pyrene, which is found in fried and smoked foods, tobacco smoke, and products of automobile fuel combustion [60, 61]. Due to the open active site, Pol κ incorporates dCMP opposite BPDE-N^2-dG adducts formed by benzo[a]pyrene with a very high efficiency and accuracy, while most DNA polymerases mainly incorporate dAMP opposite BPDE-N^2-dG, resulting in G>T transversions [57]. The knockout of the *Polκ* gene increases the frequency of mutations induced by BPDE-N^2-dG in cultured cells [62, 63].

It is important to note that the protective role of Pol κ against DNA damage can be associated with a yet unknown non-catalytic function of this polymerase. Human cells with a gene encoding catalytically inactive

Pol κ and cells with the knocked-out *POLK* gene are equally sensitive to the damaging agents, including benzo[a]pyrene [64]. In mice, both *Polκ* knockout and catalytically inactive Pol κ are associated with an increased risk of intestinal cancer induced by benzo[a]pyrene in the presence of the inflammatory agent DSS. Treatment of mice carrying the wild-type *Polκ* gene with these compounds resulted in the formation of DNA adducts and oxidized lipids (inflammation markers), but not benzo[a]pyrene products [65].

Pol κ also catalyzes DNA replication over intra- and interstrand DNA crosslinks induced by cisplatin and mitomycin C [66-68] and is involved in the repair of interstrand DNA crosslinks [69, 70], as well as DNA repair synthesis during NER [17].

Low-level Pol κ expression was observed in tumors of the rectum, breast, lungs, and stomach [71, 72]. Elevated expression of *POLK* increases the frequency of mutations in mammalian cell cultures [73, 74]. Ectopic overexpression of *Polκ* in mice causes double-stranded DNA breaks and aneuploidy and stimulates carcinogenesis in immunodeficient animals [75]. Upregulated *POLK* expression is characteristic of cells from patients with small cell lung cancer [76, 77], where it correlates with the P53 inactivation [77]. Increased expression of Pol κ is also observed in gliomas and is associated with the late stages of the disease [45].

The association of *POLK* polymorphisms with an increased risk of breast cancer has been shown (Table S1 in the Supplement). It was found that *POLK* polymorphisms affect the frequency of lung cancer development (Table S1 in the Supplement). Somatic mutations of the *POLK* gene were observed in 28% patients with prostate cancer (Table S1 in the Supplement). Many *POLK* polymorphisms have been biochemically characterized (see review [55] for more details).

Pol ζ is the only human DNA polymerase whose full-sized complex has not been isolated. The multisubunit human Pol ζ complex with an extensive deletion in the catalytic REV3 subunit was purified and characterized [14]. Pol ζ efficiently synthesizes DNA opposite cisplatin-induced intrastrand crosslinks in cooperation with Pol η [14]. Much more is known about the properties of *Saccharomyces cerevisiae* Pol ζ. Yeast Pol ζ performs efficient TLS *in vitro* in cooperation with human Pol ι, Pol η, and Pol κ and catalyzes DNA replication opposite different types of DNA damage [3]. Moreover, Pol ζ can incorporate nucleotides opposite certain lesions, thus functioning as the "inserter" enzyme. For example, Pol ζ is the main DNA polymerase carrying out highly mutagenic TLS opposite adducts caused by the carcinogenic agents aflatoxin B1 [78, 79] and aristolochic acid [80] that can be found in contaminated food and herbal preparations used in folk medicine [81]. Mutagenesis caused by aflatoxin B1 and aristolochic acid results in the development of liver and bladder tumors, respectively [82, 83]. Another feature of Pol ζ is generation of tandem mutations and mismatches during the synthesis on undamaged DNA; the most common substitutions by Pol ζ *in vivo* are G>C, G>T, G>A, and T>A transversions [3, 84].

Pol ζ plays an exceptionally important role in the replication of damaged DNA. In contrast to the Y-family DNA polymerases, whose functions are redundant, the loss of the catalytic activity of Pol ζ in mice leads to embryonic death, which points to the essential role of Pol ζ in the replication of a large number of endogenous DNA lesions [85, 86]. The loss of the REV3 function in mouse embryos is accompanied by the accumulation of DNA breaks, chromosomal instability (translocations and aneuploidy), and generalized P53-dependent apoptosis; cells with *Rev3l* mutations are extremely sensitive to DNA-damaging agents [87-89]. It is believed that Pol ζ is responsible for approximately 50% of spontaneous mutations [90].

Dysfunction of Pol ζ is associated with carcinogenesis [24, 25]. Tissue-specific conditional knockout of the *Rev3l* gene in mouse epidermal cells leads to chromosomal instability, high frequency of skin cancer, and impaired tissue regeneration [25]. A decrease in the *REV3L* gene expression in humans is associated with an increased risk of developing rectal carcinoma [91]. *REV3L* polymorphisms affect the risk of developing cancer of the lungs, breast, colon, and rectum and are associated with a negative prognosis in these diseases (Table S1 in the Supplement).

REV1 plays an important structural and regulatory role in the translesome assembly. REV1 contains sites for simultaneous binding to the Y-family DNA polymerases Pol ι, Pol η, and Pol κ (via the RIR motif) and several Pol ζ subunits [92-95]. REV1 also interacts with the non-ubiquitinated and monoubiquitinated PCNA processivity factor [96, 97]. The presence of many binding sites for polymerases and accessory factors ensures the coordination of replication enzymes and timely switching from DNA synthesis by high-fidelity DNA polymerases to translesion DNA polymerases, as well as from the synthesis by the "inserter" Y-family polymerase to the processive Pol ζ. Therefore, REV1 is a key regulator of the replication of damaged DNA.

REV1 also has weak DNA polymerase activity and predominantly incorporates dCMP opposite intact template nucleotides, AP sites, and N^2-guanine adducts [98-100]. REV1 performs C>G/G>C transversions in the SHM during maturation of immunoglobulins in B lymphocytes [20]; it may also be involved in non-targeted mutagenesis in other cells and organs (the role of REV1 in SHM will be discussed in more detail in the next section). Upregulation of *Rev1* expression in mice exposed to *N*-methyl-*N*-nitrosourea results in the REV1-dependent mutagenesis and induces intestinal adenomas [101].

Suppression of *REV1* expression by a ribozyme dramatically reduces the frequency of mutations induced by

UV and benzo[a]pyrene in cultured cells [102, 103]. Downregulation of *Rev1* expression in mice (by delivering a ribozyme-expressing plasmid using a nebulizer) reduces the frequency of chemically induced lung tumors [104]. However, deletion of the C-terminal BRCA1-like domain of REV1 (which does not disrupt the catalytic activity, but results in the loss of key protein–protein interactions in the translesome) leads to a decrease in mutagenesis, but also promotes earlier appearance of UV-induced squamous cell carcinomas of the skin [105].

REV1 polymorphisms are associated with a higher risk of development of various cancers. The amino acid substitution N373S is associated with a higher risk of developing cervical cancer, while the F257S polymorphism (rs3087386) is associated with a reduced risk of cervical cancer, but a higher risk of lung and prostate cancers (Table S1 in the Supplement). Biochemical analysis of polymorphic REV1 variants showed that the N373S protein has an increased catalytic activity when incorporating dCMP opposite undamaged G and AP sites (Table S1 in the Supplement). In breast cancer, the correlation with the tumor size and disease stage has been shown for the *REV1* polymorphisms rs6761390 and rs3792142, which are located in the promoter region and intron 5 of the *REV1* gene, respectively (Table S1 in the Supplement).

DNA POLYMERASES AND HYPERMUTATION

Cytosine deamination by the AID cytidine deaminase and subsequent removal of uracil resulting in the formation of AP site plays a key role in the mutagenesis of variable regions of immunoglobulin genes in mammalian B lymphocytes [106]. Mutations are induced mainly in the WRCY and WA motifs (W = A/T, R = A/G, Y = C/T) via dAMP incorporation opposite to uracil, error-prone TLS opposite AP sites after uracil removal by uracil DNA glycosylase UNG2, and during BER and noncanonical mismatch repair (MMR) [106].

REV1 performs G>C/C>G transversions during TLS in the SHM by incorporating dCMP opposite AP sites formed by UNG2 [20]. Pol η carries out SHM in the AT pairs. Pol η predominantly performs error-prone synthesis in the noncanonical MMR and induces A>G/T>C mutations when filling the gap created by the EXO1 exonuclease after recognition of the U-G mismatch by the MSH2/MSH6 complex [107, 108]. In addition, Pol η introduces mutations in the AT pairs in the long-patch BER following uracil removal by UNG2 and cleavage of the AP site by the AP endonuclease APE1 (MSH2/MSH6-independent synthesis) [109].

Hypermutation occurs not only in B lymphocytes. AID and APOBEC cytidine deaminases (APOBEC1, APOBEC3A, APOBEC3B, APOBEC3G) deaminate cytosines in non-lymphoid tissues. APOBEC-mediated deamination protects cells from viral infection by inhibiting the replication of retroviruses and reverse transcription of retrotransposons. APOBEC enzymes deaminate cytosine residues in genomic DNA, which can play a role in mutagenesis and carcinogenesis (including chronic viral infection conditions) [110-112]. The spectrum of mutation induced by REV1 and Pol η in the course of immunoglobulin SHM coincides with the mutation spectrum in many types of human tumors, which indicates the role of non-targeted mutagenesis induced by AID/APOBEC and REV1/Pol η in carcinogenesis [26, 29, 112]. For example, the action of cytidine deaminases and Rev1 is considered to be associated with the mutation patterns #2 and #13 found in tumors, which are characterized by C>T and C>G substitutions [26, 112]. It is assumed that the C>T transitions occur as a result of dAMP incorporation opposite uracil (by any DNA polymerase), while the C>G transversions occur when REV1 incorporates dCMP opposite an AP site after uracil removal by UNG2 [112]. AID predominantly deaminates cytosine in the WRC motif (W = A/T, R = A/G); APOBEC3G – in the CCC motif; and APOBEC1, APOBEC3A, and APOBEC3B – in the TC motif [112]. Pol η presumably induces A>G/T>C mutations in the WA motifs (W = A/T) during noncanonical MMR in actively transcribed genes [29].

REPLICATION OF DAMAGED DNA BY THE PRIMPOL PRIMASE-POLYMERASE

In addition to TLS, other cellular mechanisms exist that ensure cell tolerance to DNA damage. In 2013, human PrimPol primase polymerase was described [113, 114]. PrimPol localizes to the nucleus and the mitochondria and possesses both DNA primase and DNA polymerase activities [113]. PrimPol plays a role in protecting the cells from many types of DNA damage. It was suggested that PrimPol re-initiates replication downstream of DNA damage sites using its DNA primase activity [115-117]. In this case, a single-strand region with the lesion should be subsequently repaired, for example, by homologous recombination. In addition to its ability to synthesize DNA *de novo*, PrimPol also demonstrates the TLS activity *in vitro* and efficiently bypasses a number of common DNA lesions, such as 8-oxo-G, formyluracil, and AP sites [113, 118].

It was suggested that PrimPol exhibits the antimutagenic activity during immunoglobulin SHM and can neutralize the mutagenic activity of cytidine deaminases by reducing the frequency of C>G transversions in the leading strand [116]. The antimutagenic activity of PrimPol suggests its protective role in the prevention of carcinogenesis. *PRIMPOL* deletions are often found in patients with invasive breast cancer, and the number of point mutations in the tumors with *PRIMPOL* deletions is

almost two times higher than in the tumors without these deletions [116]. PrimPol reduces the frequency of APOBEC3B-induced mutations caused by deamination of cytosine in the TpC sites in invasive breast tumors [116]. It was suggested that initiation of DNA synthesis after AP sites by PrimPol limits the error-prone TLS opposite AP sites and stimulates a switch to a more accurate mechanism of damage tolerance involving homologous recombination [116]. A similar mechanism involving PrimPol might play a role in reducing the mutagenic potential of bulky DNA adducts. PrimPol was shown to be necessary for homologous recombination of photoproducts and benzo[a]pyrene adducts [119].

Translesion DNA polymerases play an important role in ensuring genetic stability; however, by protecting cells from DNA damage, they themselves serve as a source of mutations. Growing data suggest that error-prone translesion DNA polymerases are involved not only in carcinogenesis, but also in the development of tumor resistance to chemotherapy drugs. Specific mechanisms for the induction of mutagenesis and carcinogenesis associated with impaired functioning of translesion DNA polymerases or their uncontrolled activity remain unclear. The studies in cells and animals with knocked-out DNA polymerase genes and comparison of mutation patterns in cancer patients and model organisms using the latest advances in genome sequencing and bioinformatics are important directions in further research in this field.

Funding. The work was supported by the Russian Foundation for Basic Research (projects Nos. komfi 17-00-00264 and Bel-a 18-54-00024 for A.V.M.), by the Belarusian Republican Foundation for Fundamental Research (project No. B18R-094 for M.P.S.; Y-family DNA polymerases), and by the Russian Science Foundation (project No. 18-14-00354 for A.V.M.; PrimPol).

Conflict of interest. The authors declare no conflict of interest.

Ethical approval. The paper does not contain studies involving human volunteers and experiments performed in animals.

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