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REVIEW

DNA Polymerases and Carcinogenesis

V. M. Krutyakov[#] and T. P. Kravetskaya

Konstantinov Petersburg Institute of Nuclear Physics, Russian Academy of Sciences, 188300 Gatchina, Leningrad Region, Russia; fax: (81371) 32-303; E-mail: krav@omrb.pnpi.spb.ru

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Abstract—There are many various chromosomal and gene mutations in human cancer cells. The total mutation rate in normal human cells is $2 \cdot 10^{-7}$ mutations/gene/division. From 6 to 12 carcinogenic mutations can arise by the end of the life, and these can affect the structure of ~150 protooncogenes and genes encoding suppressors of tumor growth. However, this does not explain the tens and hundreds of thousands of mutations detectable in cancer cells. Mutation is any change of nucleotide sequence in cellular DNA. Gene mutations are mainly consequences of errors of DNA polymerases, especially of their specialized fraction (inaccurate DNA polymerases β, ζ, η, θ, ι, κ, λ, μ, σ, ν, Rev1, and terminal deoxynucleotidyl transferase, and only polymerases θ and σ manifest a slight 3′-exonuclease activity) and also consequences of a decrease in the rate of repair of these errors. Inaccurate specialized human polymerases are able to synthesize DNA opposite lesions in the DNA template, but their accuracy is especially low during synthesis on undamaged DNA. In the present review fundamental features of such polymerases are considered. DNA synthesis stops in the area of its lesion, but this block is overcome due to activities of inaccurate specialized DNA polymerases. After the lesion is bypassed, DNA synthesis is switched to accurate polymerases α, δ, ε, or γ. Mechanisms of direct and reverse switches of DNA polymerases as well as their modifications during carcinogenesis are discussed.

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During the last decade a number of inaccurate DNA polymerases have been found in eukaryotes. These polymerases are most studied in yeast and in mammals, including humans [1]. They display low accuracy in DNA synthesis on undamaged DNA template but are rather accurate on DNA lesions for which the corresponding polymerases are specific [2]. The infidelity of DNA synthesis catalyzed by these polymerases increases the probability of base mismatch and of reading frame shift. Inaccurate DNA polymerases include TdT and the repair polymerase β discovered and partially studied during the 1960-1970s [3, 4], DNA polymerase ζ found in 1996 [5], and DNA polymerases η, ι, κ, λ, μ, and Rev1 found later. By partial homology of amino acid sequences, DNA polymerase ζ belongs to family B [1], polymerases TdT, β, λ, μ, and σ to family X [6], polymerases η, ι, κ, and Rev1 to family Y, and polymerases θ and ν to family A [1]. Despite an insignificant homology of primary structure with that of classical DNA polymerases, the tertiary structure of the inaccurate polymerases has typical features of all polymerases – it forms "palm, fingers, and thumb" [2] responsible for the primer/template sorption and the moving of the DNA polymerases along DNA.

The present review considers the fundamental functional features of the above-mentioned specialized polymerases lacking corrective exonuclease (CE) activity and also of specialized DNA polymerases θ and σ manifesting this activity (table). These polymerases specifically catalyze synthesis opposite lesions in the DNA template that is not eliminated by the several repair systems. Note that some lesions of DNA template are instructive for some specialized polymerases but not instructive for others and *vice versa*. Replicative DNA polymerases α, δ, ε, and γ cannot effectively synthesize DNA opposite lesions in the DNA template (i.e. the lesions are not instructive for these polymerases) and cannot elongate primers with noncomplementary nucleotides on the 3′-end, and this results in replication block. Some specialized polymerases are able to perform elongation with accompanying overcoming of the replication block, often resulting in increased mutagenesis and carcinogenesis.

Abbreviations: AAF, *N*-2-acetylaminofluorene; AP sites, apurine and apyrimidine sites; CE, corrective 3′→5′-exonucleases; PCNA, proliferating cell nuclear antigen; sumo, small ubiquitin-like modifier; TdT, terminal deoxynucleotidyl transferase.

[#] Deceased.

Specialized eukaryotic DNA polymerases

Greek name	HUGO name	Primary sequence class	Associated 3′→5′-exonuclease	Putative main function
β	POL B	X	absent	Base excision repair; synthesis opposite lesions in DNA template; role in embryogenesis
ζ	POL Z	B	absent	Elongation of incorrect primers; role in embryogenesis
η	POL H	Y	absent	Accurate synthesis opposite lesions in DNA template; is inactivated in variant *xeroderma pigmentosum*
θ	POL Q	A	present	Repair of crosslinks between DNA strands; synthesis opposite AP-sites
ι	POL I	Y	absent	Synthesis opposite lesions in DNA template; the most inaccurate polymerase breaks the Watson–Crick's rule; hypermutability
κ	POL K	Y	absent	Base substitutions and minimal deletions; somatic hypermutability
λ	POL L	X	absent	*De novo* synthesis; moderate activity of TdT; synthesis opposite lesions in DNA template
μ	POL M	X	absent	Minimal deletions; *de novo* synthesis; moderate activity of TdT
σ	POL S	X	present	Participates in cohesion of sister chromatids; repair of double-stranded breaks
ν	POL N	A	absent	Synthesis opposite thymine glycols
–	Rev1 L	Y	absent	Synthesis opposite AP sites, dCMP transferase
–	TdT	X	absent	DNA template-independent polymerase; hypermutability of antibody genes

EXTREMELY INACCURATE POLYMERASES

Terminal deoxynucleotidyl transferase (TdT) from calf thymus has molecular weight 32 kDa and consists of two subunits with molecular weights of 24 and 8 kDa. In adult animals TdT is found only in the thymus but not in other lymphoid tissues or leucocytes. But during embryogenesis TdT is immunochemically detected in nearly all tissues [7]. TdT does not need DNA template and links each dNTP to the 3′-end of single-stranded DNA. Therefore, in double-stranded DNA it is suggested to misincorporate at a frequency of $7.5 \cdot 10^{-1}$, because on average one of four dNTPs can be complementary to the DNA template. TdT is thought to contribute to hypermutability of the immunoglobulin genes [7]. As differentiated from DNA polymerase α, TdT is able to synthesize DNA opposite UV-caused lesions in the DNA template [7] because to be active it needs only DNA primer, and the template features are not important.

DNA polymerase β has molecular weight of 39 kDa and is mainly localized in the chromatin of mammalian cells [8, 9]. This polymerase fills short single-stranded gaps in DNA, is distributive, i.e. joins one nucleotide per each sorption on DNA (but is processive on breaks of 4-6 nucleotides in length [10]), and plays an essential role in the excision repair of small gaps in DNA [1]. It displays activities of 5′-deoxyribosophosphatase and DNA lyase [11] that is necessary for ligation of the filled gap in DNA. Knockout of the polymerase β gene in mice results in the death of the animals immediately after birth [12]. DNA polymerase β makes errors (base substitution plus reading frame shift) at a frequency of 10^{-3} on filling elongated

gaps [13]. During excision repair of single nucleotides, the DNA polymerase β rate of errors is $(3\text{-}5)\cdot10^{-4}$ [14]. This polymerase can bypass lesions in UV-irradiated DNA template, in particular thymine–thymine cyclobutane dimers and thymine–thymine pyrimidine–pyrimidone (6-4) photoproducts [15]. DNA polymerase β is also involved in recombination, meiosis, and neurogenesis [16]. As discriminated from DNA polymerases α, δ, and ε, polymerase β effectively overcomes *in vitro* the modified region of DNA d(GpG)-*cis*-platinum [17]. DNA polymerase β also can replicate *in vivo* DNA containing unrepaired O^6-methylguanines; it inserts dTMP opposite O^6-methylguanine preferentially as compared to dCMP [18].

DNA polymerase η has molecular weight of 78 kDa in human and 70 kDa in yeast [16]. In human this polymerase is a product of the gene that is mutant in patients with variant *xeroderma pigmentosum* (XP-V). This mutation is associated with a predisposition to skin cancer [19] because in the absence of DNA polymerase η DNA synthesis opposite pyrimidine dimers after insolation is catalyzed by other inaccurate polymerases. DNA polymerase η often makes errors on an undamaged DNA template (10^{-3}-10^{-4}) [20] but manifests a very high accuracy of synthesis on certain types of DNA lesions [21]. Polymerase η inserts correct nucleotides during synthesis opposite thymine dimers, *cis*-platinum, or AAF-adducts [22] and is rather accurate in synthesis opposite O^6-methylguanine [23]. This polymerase elongates a product of the correct synthesis but stops upon its own error; it makes errors during synthesis opposite 8-oxoguanine, AP-sites, and (+)-*trans*-anti-benz(a)pyrene-N^2-dG [24, 25]. During synthesis opposite AP-sites, polymerase η inserts dAMP in 70-80% of cases and in 10-25% of cases causes single nucleotide deletions [26]. DNA polymerase η interacts physically with DNA polymerase ι (see below), and the two polymerases are accumulated within replication forks [27, 28].

DNA polymerase κ overcomes AAF-adduct without errors and inserts C or T and to the lesser degree A and (−)-*trans*-anti-benz(a)pyrene-N^2-dG-adduct where it preferentially joins C opposite the lesion [29]. DNA polymerase κ makes errors at a frequency of $0.5\cdot10^{-2}$ [30], but according to data presented in [31] on undamaged DNA it makes errors at a frequency of $7\cdot10^{-3}$ during base substitution and of $2\cdot10^{-3}$ during deletion. This polymerase catalyzes T→G transversion at the probability of 10^{-2} [30] and also makes errors during synthesis opposite AP-sites and 8-oxoguanine [30]. Polymerase κ is moderately processive (25 or more nucleotides per sorption on DNA), which indicates its significant role in spontaneous mutagenesis [31]. Human polymerase κ has molecular weight of 99 kDa [30]. Under the influence of NO, 2′-deoxyxanthosine is produced in DNA. DNA polymerases α and β stop before this lesion, whereas polymerases η and κ easily bypass it and opposite the lesion mainly insert the incorrect dTMP, and less frequently the correct dCMP [32].

DNA polymerase ι is the most inaccurate polymerase; it mainly misincorporates G instead of the correct A opposite T in DNA template [33, 34]. This seems to disturb the Watson–Crick rule that for supporting the regular spiral structure of both DNA chains the pyrimidine base residue of one chain must be placed opposite the purine base residue of the other chain; this can be realized only on formation of A with T and G with C pairs stabilized by hydrogen bonds. The number of errors is the highest on the poly(dT) template when G is misincorporated three times more frequently compared with the correct incorporation of A, and T is misincorporated at a frequency of $7\cdot10^{-1}$ [33]. It seems that the incorporation of G opposite T is necessary during synthesis opposite methylcytosine, when the latter is converted into T after deamination. DNA polymerase ι synthesizes GA opposite thymine dimer instead of the correct AA and thus elongates the resulting incorrect primer [35]. As discriminated from the DNA polymerases η, κ, and β, polymerase ι stops before 8-oxoguanine in the template and mainly incorporates G opposite AP-sites [34]. DNA polymerase ι seems to participate in excision base repair because it displays activity of 5′-deoxyribosophosphatase similarly to DNA polymerases β and λ [36]. Expression of the 81-kDa DNA polymerase ι is increased in mammary gland carcinoma cells, especially upon their UV treatment [37].

INACCURATE DNA POLYMERASES AND GENOME STABILITY

Thus, specialized DNA polymerases, except polymerases θ and σ, are too inaccurate, and polymerase ι even disturbs the Watson–Crick rule, inserting G and T opposite T (see above). Frequencies of their errors, especially on undamaged DNA are $7.5\cdot10^{-1}$ for TdT and DNA polymerase ι and to 10^{-3} for DNA polymerase β that should result in "error catastrophe", because the frequency of spontaneous mutagenesis calculated per replicated nucleotide is 10^{-10}-10^{-12} [38, 39]. The low rate of mutagenesis cannot be sufficiently explained even by the respectively high accuracy of DNA polymerases δ and ε (10^{-5}-10^{-6}) [13] on taking into account activities of the replication and post-replication systems correcting DNA polymerase errors and existence of neutral mutations [40]. But a very low accuracy of specialized DNA polymerases, especially of TdT, ι, and κ, is surprising because the mutagenesis induced by such level of inaccuracy is incompatible with cell survival, at least in prokaryotes [41]. How do cells neutralize the strikingly low accuracy of specialized DNA polymerases leading to carcinogenesis and retain their survival-supporting ability for synthesis opposite lesions in the DNA template? At present,

there is no clear answer to this question, but some finding-based hypotheses seem to be reasonable.

First of all, these polymerases are not found in every tissue. Thus, in young organisms TdT is detected only in the thymus [3], although some specialized polymerases are required for the organism's life, especially during embryogenesis when the repair systems are not developed in time for elimination of multiple DNA lesions before a rapid start of the next round of replication.

The replication stops before the lesion in DNA template. In eukaryotes the protein PCNA acts as a factor of processivity, i.e. of uninterrupted synthesis of DNA. Upon the stop of replication one molecule of the protein ubiquitin joins to Lys164 (one of three lysine residues exposed within PCNA) under the influence of corresponding ligases. This weakens the binding of accurate DNA polymerases with PCNA and increases its affinity for inaccurate polymerases. At least five inaccurate polymerases (β, η, ι, κ, λ) are capable of reversible joining to PCNA [42]. As a result, accurate replicative DNA polymerases earlier bound to PCNA are substituted by one of the specialized polymerases depending on the lesion character, and the replication is recommenced [43]. Sumoylation acts on PCNA similarly but more rapidly [44]. Sumo (small ubiquitin-like modifier) is a protein responsible for the covalent modification of many cell proteins. Sumoylation is a dynamic process mediated by activating, joining, and binding of enzymes, which is easily reversible under the influence of specific proteases. When specialized DNA polymerases bypass the DNA lesion, ubiquitin or sumo dissociate from PCNA under the influence of corresponding proteases (centrins) [45]. In some cases the loss of the regulatory control of sumoylation/desumoylation leads to carcinogenesis and metastasis [46-48].

Then, the cells should not allow specialized polymerases to effectively operate on undamaged DNA where they are especially inaccurate. After bypassing a lesion on the DNA template and limited elongating an incorrect primer, it is necessary to switch catalysis of DNA synthesis from specialized polymerases to the accurate DNA polymerases δ and ε as quickly as possible [49].

In higher eukaryotes only 5% of the genome is transcribed [50], which allows them to survive excess mutagenesis in non-informative DNA. The survival strategy of unicellular organisms is supported by rapid multiplication, in particular, through overcoming replication blocks on DNA lesions with involvement of specialized DNA polymerases, even at the price of increased mutagenesis. In fact, the death of 10-20% of the population of unicellular organisms as a result of the total mutagenesis is not intolerable. But in the surviving fraction of the population useful mutations can appear, and these will be consolidated during evolution due to natural selection. But multicellular organisms present quite another situation. Their survival strategy is provided for by the variety and complication of the organism's functions. An increased level of mutagenesis caused by activities of inaccurate specialized DNA polymerases can result in carcinogenesis. It is known that a precancer cell is mutable, i.e. prone to variability, and is characterized by an increased rate of spontaneous mutagenesis [51, 52]. In the genome of such a cell among thousands of different mutations five to seven mutations can arise that can activate protooncogenes, or inactivate genes encoding suppressors of tumor growth, and also damage genes of proteins which increase the accuracy of DNA synthesis, including CE and proteins of post-replication duplex correction (mismatch repair). These events promote conversion of a normal cell into a cancer cell. Therefore, for multicellular organisms the death of a fraction of cells as a result of long-term replication block in the place of DNA lesion (promoted by increased expression of CEs) is more advantageous than the death of the whole organism because of cancer. Superproduction of cloned CEs in *E. coli* suppresses 10-100-fold the spontaneous and induced mutagenesis [53, 54], and this makes promising similar works with mammalian cell cultures. At present such works are stimulated by cloning genes of human and mouse major CEs [55, 56].

Results of the first studies on accuracy of DNA polymerases from normal and tumor cells were various and contradictory and did not allow definite conclusions [57, 58]. Later the picture became clearer. An increased activity of DNA polymerase β was found in humans in malignant tumors of the large intestine [59], prostate [60], urinary bladder [61], and in leucosis [62], as well as in mouse tumors [63, 64]. In cancer cells some mutants of this reparative polymerase were found, and their accuracy was twofold lower than the accuracy of the wild type polymerase β [65-67].

Superproduction of some specialized DNA polymerases (β, λ, ι, κ) has been studied in different tumors [67]. Production of these polymerases was more than twofold higher than normal in 45% of 68 tumors studied. Overexpression of DNA polymerase β has been confirmed by studies on both its mRNA and the polymerase itself in one third of tumors studied, especially in tumors of uterus, prostate, and stomach [67]. A transgenic mouse has been recently created which carries an inactivated CE within the major elongating DNA polymerase δ. In mice homozygous in this defect various epithelial cancers developed that were not found in the corresponding heterozygotes [68].

In the human genome 10^5 spontaneous lesions occur in DNA within 24 h as a result of deamination, depurinization, oxidation, and incorrect methylation [69]. Each lesion leads to DNA replication block. This block is overcome by DNA repair or due to activities of 10 different specialized DNA polymerases capable of synthesizing DNA opposite certain lesions in the DNA template, and this is fraught with mutagenesis and carcinogenesis because of decreased accuracy of these polymerases.

If an error in DNA biosynthesis is not removed under the influence of CEs and the synthesis continues, a heteroduplex is produced that later can be eliminated by a post-replication system of heteroduplex correction (mismatch repair). This system consists of products of four genes: *hMSH2*, *hMSH6*, *hMLH1*, and *PMS2*. Mutants of any of these genes manifest signs of genome instability and, correspondingly, of an increased rate of carcinogenesis [70].

Autonomous (individual) CE not bound covalently with DNA polymerases increase their accuracy both *in vitro* and *in vivo* [40]. The role of their possible inactivation in carcinogenesis is still unknown. CEs are found to increase up to 30-fold the accuracy of DNA polymerases α [71], β [72], and δ [73] by forming complexes with these polymerases. At present, in our laboratory the activities of these exonucleases in normal and cancer cells of rodents and humans are under study.

Thus, errors of DNA polymerases during synthesis of protooncogenes or genes encoding suppressors of tumor growth can be a cause of carcinogenesis. The cells taking this path became mutant in genes encoding proteins responsible for genome stabilization. Such mutations decrease the accuracy of DNA synthesis and the efficiency of repair of synthesis errors. Such cells called mutators are characterized by an increased rate of spontaneous and induced mutagenesis that finally results in malignization of these cells [57, 74]. An earlier explanation of the mutator phenotype of cancer cells was as follows [75]: such a phenotype is a result of repeated rounds of selection of a mutant cell, which has advantages for growth in the organism. This allows the progeny of this cell to proliferate and create a tumor also manifesting other mutator features if they provide for additional advantages for multiplication in the given organism.

Thus, genomic and chromosomal instability can lead to a malignant tumor that concurrently possesses the following main features: unlimited number of divisions ("immortality"), absence or shortening of the G_0 stage of the cell cycle, absence of contact inhibition of division, invasiveness and metastasizing, enhanced role of glycolysis, and multiple drug resistance. Various normal cells have separately some properties of the cancer cell, and this makes it difficult to specifically target cancer cells. The infidelity of DNA polymerases results in constant mutating of cells within tumors and metastases, which explains their capability of escaping different regulatory limitations superimposed by the multicellular organism and also escaping radio-, chemo-, and immunotherapy, and seems to lower the efficiency of target therapy directed to an affected organ.

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