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Atypical DNA Polymersases in Oncogenesis: *Mini-Review*

Vadim Davydov[1], Alexander Bukhvostov[2], Olga Kamkina[3], Dmitry Kuznetsov[2*]

[1]Department of Biochemistry and Molecular Biology, Pirogov Medical University, Moscow, Russia
[2]Department of Medical Nanobiotechnologies, Pirogov Medical University, Moscow, Russia
[3]Department of Physiology, Pirogov Medical University, Moscow, Russia
Email: *kuznano@mail.ru, vaddavydov@mail.ru, olga.pharma888@rambler.ru, tanzbukh@gmail.com

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Abstract

The aim of a present study is to perform a brief but clear comparison of numerous and controversial data published in the past 20 years which were focusing on the significance of structural and catalytic peculiarities of the DNA repair related Polymerases in cancer cells, as these enzymes may serve as the possible targets for new cytostatic pharmacophores. Thus, with this respect, some specific inhibitors of these enzymes such as paramagnetic divalent metal cations ($^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$) and the ultrashort single-stranded DNA fragments are considered as a new, promising group of anti-cancer agents.

Keywords

Unique Cancer Enzymes, DNA Synthesis and Repair, Medicinal Enzyme Inhibitors, Magnetic Isotope Effects, Spin-Selective Enzymology

1. Introduction

DNA Polymerase is an enzyme that catalyzes the synthesis of a DNA polynucleotide chain and is involved in the processes of DNA replication, repair, and recombination. Eukaryotic cells produce about 16 types of DNA Polymerases that take part in DNA biosynthesis and its repair [1].

The structure of DNA Polymerases of different species is very conserved. Structurally (architecturally), the enzymes' appearance reminds that of a right hand with three main subdomains: the palm, the fingers, and the thumb. The DNA-binding site is located in the cavity between them. The catalytic center is represented by a conserved amino acid sequence in the "palm" subdomain. The "fingers" bind 2'-deoxynucleotide triphosphates, and the "thumb" binds DNA. The greatest conservatism of the amino acid sequence is typical for the "palm", while

for the other domains (the "fingers" and "thumb"), the amino acid sequence is more variable [2].

According to phylogenetic analysis and molecular structure data, all DNA Polymerases may be subdivided into several families: A, B, C, D, X, Y, and RT [2].

In the most recent publications, a special link between evolutional diversity of this type of enzymes and their involvement into variable oncogenesis tracks has been revealed and emphasized [3]-[7]. Thus, those *β*-like DNA Polymerase species which were found of being the structurally simplest ones (17.5 - 33.0 kDa monomers), are usually hyperexpressed in malignancies which makes them legitimate targets for cytostatics as long as the latter suppresses a specific activity of these enzymes *in situ* [8]-[11]. In particular, paramagnetic isotopes of divalent metal ions ($^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$) might have an essential impact on DNA pol*β*-directed catalysis due to Magnetic Isotope Effects (MIE) and, hence, they should attract an attention as the promising anti-cancer agents [11]-[13].

As seen from one of the most recent (and the most «intriguing») publications on spin selective metal-dependent enzymatic catalysis, the ion-radical mechanism is indeed beyond the truly efficient magnetic control over molecular pathogenesis of malignancies [14]. This itself attracts a special attention to magnetic isotope effects manifested by ^{25}Mg, ^{43}Ca and ^{67}Zn nuclei once a DNA synthesis/repair is the case [12] [14]-[16]. So there is a lot of sense to assume that the metal involving DNA Polymerase activities is about to get operated through a spin selective magnetic mechanism which makes possible to consider these enzymes as the legitimate targets for anti-cancer therapies.

2. The Structure and Properties of DNA Polymerases *β*

DNA Polymerase *β* (pol*β*) belongs to the X family, which is represented by a group of enzymes involved in the synthesis of single-stranded DNA (ssDNA) fragments [17]. Pol*β* catalyzes the synthesis of short ssDNA chains at a low rate, but with a high degree of copying accuracy [17]. This property is of fundamental importance for a cell, providing the neat repair of damaged DNA [18].

Pol*β* is encoded by the *POLB* gene, which expression is controlled by the CREB1 transcription factor associated with the adenylate cyclase signaling system [19]. Pol*β* is a metalloenzyme with magnesium cations in its active center [20]. It consists of one polypeptide chain of 335 amino acid residues and has the smallest mass among other DNA Polymerases, namely, 33 - 55 kDa [1] [20] [21]. The isoelectric point of this enzyme is in the pH range between 8.3 - 8.7.

A characteristic feature of pol*β* is its resistance to the inhibitors of other DNA Polymerases: the so-called *N*-ethylmaleimide and aphidicolin. Also, unlike DNA Polymerases of other types, pol*β* is unable to hydrolyze the terminal 3',5'-phosphodiester bond [17]. Under optimal conditions, the enzyme catalyzes the synthesis of relatively small single-stranded DNA fragments consisting of 200 - 300 nucleotide residues at a low rate [22].

In the molecule of pol*β* two functionally significant regions are distinguished:

the polymerase and the lyase ones (**Figure 1**) [20] [21]. The lyase activity of the enzyme is associated with the N-terminal domain. The polymerase domain consists of three separate subdomains: C (catalytic), D (DNA-binding), and N (binding site of an inserting nucleotide).

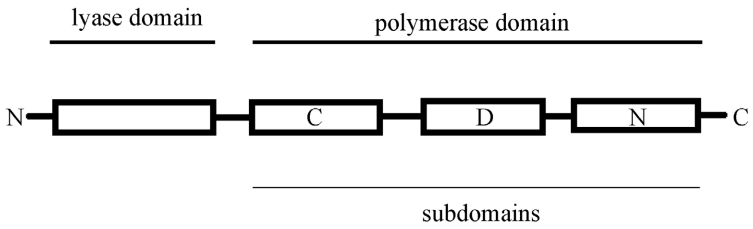

Figure 1. The domain structure of the polβ molecule [7].

Two divalent metal cations of Mg^{2+} are associated with the catalytic subdomain [20], though, according to some authors, there are three Mg^{2+} ions [23]. Mg cations are necessary to maintain the "closed" active complex of the enzyme and to ensure the accuracy of a nucleotide insertion during the repair of an altered polynucleotide chain [18]. This reaction also involves sodium cation (Na^{+}), which takes part in decreasing the energy barrier of the DNA-Polymerase reaction [23].

Phosphorylation of polβ at Ser-44 by protein kinase C leads to a change in the conformation of its polypeptide chain: the transition from the "closed" (active) state to the "open" (inactive) state. As a result, the polymerase activity decreases. However, polβ phosphorylation does not impair its ability to bind DNA [18] [21]. The coordinating effect of Mg^{2+} cations in the active site of the enzyme plays a pivotal role in the conformational changes caused by the phosphorylation of the polypeptide chain [18] [24].

In a cell, polβ is eliminated by ubiquitination and subsequent hydrolytic degradation in proteasomes [25].

The enzyme takes part in a specific DNA repair mechanism, namely, the Base excision repair (BER). During BER, polβ replaces a nucleotide containing a modified or absent nitrogenous base in the polynucleotide chain. Such DNA damages appear under the effect of ionizing radiation and/or various mutagens (chemical carcinogens) [26].

3. β-Like DNA Polymerases from Tumor Cells: The Peculiarities of the Structure, Properties, and Their Role in the Oncogenesis

In view of the fact that polβ provides the repair of damaged DNA, failing which may result in mutations and malignant conversion, this enzyme acts as a tumor suppressor [20] [26]-[28]. Therefore, the variants of polβ with altered structure and properties, such as low accuracy of copying the polynucleotide chain or reduced catalytic activity of the enzyme, may result in tumorigenesis [20] [29].

The gene expression of this enzyme in malignant tumor cells is usually elevated,

and the overexpression correlates with a poor prognosis for the patients [30]-[37]. Apparently, such a shift in gene expression is a specific manifestation of the increased expression of different families of DNA Polymerases (*POLE*, *POLD1*, etc.), as result of their mutation in patients with cancer (colorectal cancer, ovarian cancer, uterine cancer, etc.). The detection of such mutations is used in clinical medicine for a primary assessment of the tumor immunotherapy effectiveness and prognosis [38] [39].

30% - 40% of human tumors express various variants of polβ, which can differ from each other significantly in their primary structure [25] [33] [40]. These forms of the enzyme usually possess reduced catalytic activity, providing less effective DNA repair. This underlies the genome instability and subsequent tumor development [40]. Even the mutations in the promoter region of the polβ gene were found to accompany the malignant neoplasms [41].

There are known enzymes that have properties characteristic to the classical DNA Polymerases β and yet, differ from the latter in their structure and catalytic properties. Sometimes they have a larger molecular mass (up to 260 kDa), in comparison to the classical variants of polβ, and are designated as β-like DNA polymerases [17] [30] [42]. Their presence in tumor cell cultures is widely reported [30] [43] [44].

Thus, in two human retinoblastoma cell lines, WERI-RB-1 and Y-79, β-like DNA Polymerases similar in structure and properties are detected. They have a molecular mass of 23.5 kDa and isoelectric point (IEP) values of 8.5 and 8.2, respectively [30]. Like classical DNA Polymerases β, they are monomeric proteins with two active sites, each of which is coordinated by the Mg^{2+} [44].

β-like DNA Polymerase from human acute myeloid leukemia HL-60 cells has an IEP typical for chromatin proteins (8.45). The polypeptide chain of the enzyme contains a lot of arginine and lysine residues and has the molecular mass is about 66.5 kDa. The molecule has a globular shape and contains many α-helical domains. The pH optimum for the enzyme is 8.0. *Km* for dTTP is 0.016 mM and *Kcat* is 0.622 μM dTTP/min/mg protein. The replacement of the Mg^{2+} in the active site with a nonmagnetic $^{40}Ca^{2+}$ cation has an inhibitory effect on the enzyme. However, in this case, only one of the two Mg^{2+} is replaced by Ca^{2+} cation [17] [45].

Similar to classic DNA Polymerases β, β-like DNA Polymerases are resistant to *N*-ethylmaleimide and aphidicolin. At the same time, the enzymes are subjected to activation by high concentrations of potassium chloride and to inhibition by ddTTP (dideoxythymidine triphosphate) [23] [25] [32]. Like other DNA Polymerases β, they do not have exonuclease activity and, judging by the data of the kinetic parameters study, they have a relatively low processivity [45], synthesizing short single-stranded polynucleotide molecules consisting of 40 - 300 nucleotide residues [46].

At the same time, β-like DNA Polymerases from different cancer cell lines, despite a similar molecular mass (23 - 24 kDa), have some specific features dictated by the differences in the primary structure. This can be confirmed by the differences in the IEP of β-like DNA Polymerases from WERI-RB-1 and Y-79 cells (8.5

and 8.2, respectively) [30].

Differences in the structure of *β*-like DNA Polymerases from the two retinoblastoma cell lines are accompanied by the peculiarities in the kinetics and regulation, which manifest in different *Km* values for dTTP. Thus, the enzyme from WERI-RB-1 cells has a higher affinity to this substrate, compared to that from Y-79. Besides, the two enzymes respond differently to ddTTP and KCl [30].

The activity of *β*-like DNA Polymerases depends on the concentration of reduced iron cations (Fe^{2+}) in the incubation medium. Thus, the activity of the enzyme isolated from HL-60 cells decreases threefold at 15 mM of Fe^{2+} in the medium. Similar effects are revealed for *β*-like DNA Polymerases from different retinoblastoma cell lines. It was demonstrated that iron cations (Fe^{2+}) replace Mg^{2+} in the active site of the enzyme [44].

According to the results of the studies with gel filtration, the enzyme undergoes oligomerization under the influence of reduced iron cations, forming dimeric, trimeric, and tetrameric molecular complexes [43].

3.1. Substrate Oversaturation Effect

Interestingly, some *β*-like DNA Polymerases are able to carry out non-template synthesis of short (up to 300 *n*) polydeoxyribonucleotides under the conditions of supersaturation with nucleoside triphosphates (50 mM - 200 mM) in the incubation medium [34] [47] [48]. Although the mechanism of this phenomenon is still unclear, the process seems alike to the 3'-terminal polyadenylation of mRNA precursors [49]. The magnetic isotope effect (MIE) of $^{25}Mg^{2+}$ cations in the cytoplasm of tumor cells (HL-60, WERI-1A, and Y-79) can manifest in the hyperproduction of ATP due to a direct impact on the functioning of nucleotidyl kinases (creatine kinase, pyruvate kinase, etc.), thus creating conditions for supersaturating the intranuclear pool with 2'-deoxyribonucleotide triphosphates (dNTPs) and, accordingly, for initiating non-template polymerization of the latter. This, in turn, contributes to a cytostatic effect due to the decreased efficiency of DNA repair [15] [50]-[52].

As seen from above, very few of the *β*-like polymerases ever tested are indeed capable of being promoting such an unusual, merely "abnormal", catalytic behavior [15] [47]-[52]. It looks like this depends on unique structural peculiarities—3D simplicity [6] [12] [53] and the high ionic strength (4.0 - 8.5 SSC) catalytic resistance [13] [54] *in vitro*. Noteworthy, despite of their obvious chemical-enzymological significance, these findings are meaningless in terms of the *in vivo* related scenaria. Taking into account an extremely high level of dNTP concentration required, it is hardly possible to assume any physiologically realistic situation leading to a non-template DNA fragments formation [13] [53] [55]. So there is no a reliable pharmacological potential beyond.

3.2. The Inhibition of *β*-Like DNA Polymerases as a New Approach in the Chemotherapy of Tumors

As was mentioned above, in the cells of malignant tumors, the overexpression of

β-like DNA Polymerases leads to the increased biosynthesis rate of these enzymes. As a result, DNA is resistant to damage (mutations), and tumor cells acquire high viability and proliferative potential. In cancers, the limited efficiency of DNA repair (BER) mediated by pol*β* predetermines genome instability [56]. That is why this type of DNA Polymerases is considered as a target for anti-cancer drugs [44] [52] [56]-[59]. In this regard, the search for the effective inhibitors of these enzymes or the suppressors of their synthesis seems to be a promising area of pharmacological exploration.

To block DNA repair, antimetabolites, such as the various derivatives (analogues) of dNTP [15], can be used as pol*β* inhibitors, along with the irreversible ones [56] [59]-[61]. However, the high cytotoxicity of such inhibitors limits the possibility of their clinical application. At the same time, the paramagnetic cations of divalent metals are promising inhibitors of *β*-like DNA Polymerases [46] [62] [63].

3.3. Nuclear Spin-Selective Path in DNA pol*β* Functioning

A highly selective inhibitory effect of spinless paramagnetic nuclei of some metal isotopes on catalytic activity of *β*-like DNA Polymerases is based on the MIE. The replacement of the "non-magnetic" magnesium isotope in the active center of the enzyme by $^{25}Mg^{2+}$ decreases the enzyme's activity, which manifests in the reduced rate of ssDNA synthesis and length *in vivo*. As a result, the contribution of *β*-like DNA Polymerases to DNA repair in tumor cells is limited, thereby reducing their proliferative activity and viability. The inhibitory effect of the paramagnetic isotopes of $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ on *β*-like DNA Polymerases was demonstrated on human acute myeloid leukemia HL-60 cells and retinoblastoma cells [15] [46] [64]-[66].

The decline in the activity of these enzymes naturally leads to a reduced efficiency of their functioning. In the presence of the paramagnetic cation in the incubation medium the enzyme synthesizes shorter ssDNA fragments [46] [66] [67]. However, the inhibitory effect of the paramagnetic divalent cations on *β*-like DNA Polymerases can be sharply reduced by increased Fe^{2+} concentration in the medium. As a result, the action of such cations is limited in tissues rich in endogenous iron. For instance, in the cells of liver and spleen in mammals, the inhibitory effect of the paramagnetic cations does not appear at all [68].

As stated above, this is the MIE which underlies the effect of the paramagnetic $^{25}Mg^{2+}$ cation on *β*-like DNA Polymerases. The enzymatic process of the addition of a 2'-deoxyribonucleotide residue to a polynucleotide chain occurs not only via the classical reaction of nucleophilic substitution, but can also be associated with the formation of a radical ion intermediate. In the formation of the latter the magnesium cation is involved (**Figure 2**) [62]. In this process, an electron from $3'O^-$ within the 2'-deoxyribose residue is transferred to the metal cation. This is a key step in the DNA synthesis, resulting in the formation of a radical-ion pair [$3'O^{\cdot}$ and Mg^+] and further attachment of the oxyradical to the double bond of P*α* = O

2'-deoxyribonucleotide triphosphate. With that, a pyrophosphate is released. It is the participation of the magnesium cation in the reaction catalyzed by polβ, coupled with the radical ion mechanism, that determines the possibility of MIE formation and, thus, the "spin-sensitive" nature of this process [15] [69].

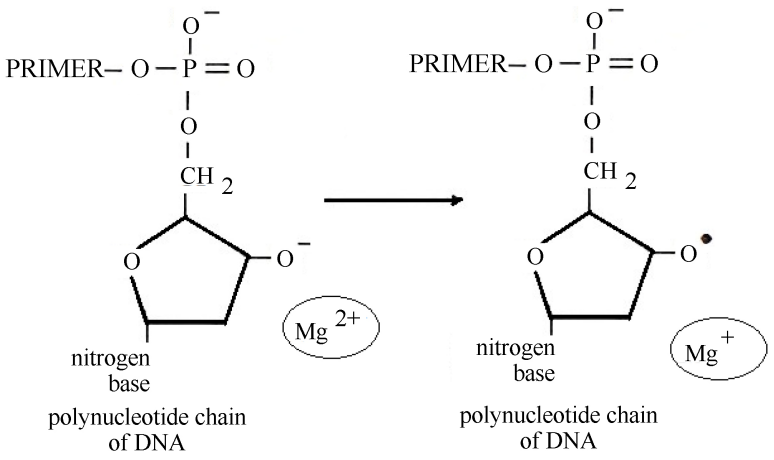

Figure 2. The formation of a radical-ion product during the DNA Polymerase reaction [62].

Besides, the reaction catalyzed by β-like DNA Polymerases can be modulated by the external magnetic field. In the studies on HL-60 cells, the synthesis of single-stranded polynucleotide molecules by β-like DNA Polymerases was shown to be inhibited under the influence of the external magnetic field with 1000 - 1500 H inductance. Furthermore, the presence of a paramagnetic magnesium cation ($^{25}Mg^{2+}$) in the incubation medium significantly enhanced this inhibitory effect [53] [69].

A mechanism is proposed to explain this phenomenon. According to [30] [69], an interaction occurs between the "magnetic" nuclei of the divalent metal, which act as electron acceptors forming a radical-ion pair with the oxygen of a phosphate group (electron donor) due to an ultrafine Coulomb effect on the paramagnetic domain. In the process, the "magnetic" cation induces a singlet-triplet transition of the radical-ion pair [12]. The ion-radical intermediate that appears during the reaction can then easily recombine to form the initial reactants or undergoes ST-conversion. As the rate of the ST-conversion increases, the rate of the enzymatic reaction increases as well. Therefore, that very stage of the reaction is "spin-sensitive". Moreover, when the non-magnetic $^{24}Mg^{2+}$ is replaced by the paramagnetic $^{25}Mg^{2+}$ and/or under the influence of an external magnetic field of a certain inductance, the rate of the ssDNA synthesis by β-like DNA Polymerases slows down [13] [53].

As a result of the inhibitory effect of the paramagnetic cations on β-like DNA Polymerases, the single-stranded polynucleotides synthesized become much shorter than normal ones and consist of only 40 - 100 2'-deoxyribonucleotide residues [46]. This is not enough for the full process of DNA repair in tumor cells

[62]. Besides, the short ssDNA fragments also possess inhibitory properties, thus enhancing the inhibitory effect of the paramagnetic cations.

In this way, by inhibiting the activity of β-like DNA Polymerases, $^{25}Mg^{2+}$ contributes to the antitumor effect [12] [15] [17] [25] [30] [33] [43]-[46] [63] [64] [66]-[71].

3.4. Pharmacological Potential of the Magnetic Isotope Effects on DNA polβ Targets

The pharmacological potential of the paramagnetic isotopes of the divalent metal cations ($^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$) as cytostatic agents targeting β-like DNA Polymerases can be applied for anticancer therapy, though the certain data describe below should be taken into account [6] [11] [13] [53] [55].

First, there is an issue of the targeted delivery of the paramagnetic ions to the tumor cells and, accordingly, the selectivity of their accumulation in the "center of malignancy" [15] [50] [72] [73]. This can be achieved both through the use of porphyrin-fullerene cation-exchange nanoparticles of the PMC16 family (**Figure 3**) [15] [50] and through "non-Markovian discrimination". The PMC16 nanoparticles have high affinity to porphyrin-signaling proteins on the mitochondria outer membranes of lymphoblasts, promyelocytes, and acute myeloblastic leukemia cells [73] [74]. The "non-Markovian discrimination" means the preferential accumulation of the amphiphilic nanoparticles (such as PMC16) in the intensively growing tumor tissue ("expanding reservoir"), compared to the neighboring area of the normal tissue not characterized by invasive growth [72] [75].

The second issue is the mobility of chromatin, which limits the availability of the targets from among its protein components, such as β-like DNA Polymerases. This, in turn, contributes to the selectivity of the cation-protein interaction, which occurs during a short interphase typical for most tumor cells [76] [77].

In a majority of the DNA polβ-devoted works, a non-monomeric subunits possessing structure does not fit a MIE-centered hypothesis of a nuclear spin selective suppression of magnesium-dependent DNA repair in malignant tumors [3]-[6] [8]-[10]. This, nonetheless, is in a good favor with some DFT and X-ray crystallographic models showing that only a relatively small amounts of enzyme species, β-like ones, characterizes by "unusually short" (5.0 - 7.0 nm) distance between the catalytic site coordinated magnesium ion (electron acceptor) and the phosphate oxygen (electron donor) which is a critical condition for Coulomb-related singlet-triplet conversion within a resulted ion-radical pair [7] [13] [53]. That explains a high selectivity of some β-like Polymerases as the MIE participants and therefore, as a potential targets for paramagnetic ion-cytostatics ($^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$) [7] [11] [53] [78].

As follows from a number of researchers, the amphiphilic nanocationites based on porphyrin adducts of fullerene-C_{60} [51] [75] [79] and carboxymethyl hydroxyapatite [51] [74] may serve as promising pharmacophores that meet the criteria for ensuring targeted *in vivo* delivery of $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ cations into the

cells of human tumors transplanted into animals, such as B16 melanoma, P388 leukemia, and LLC 27 (Lewis lung carcinoma) [7] [55].

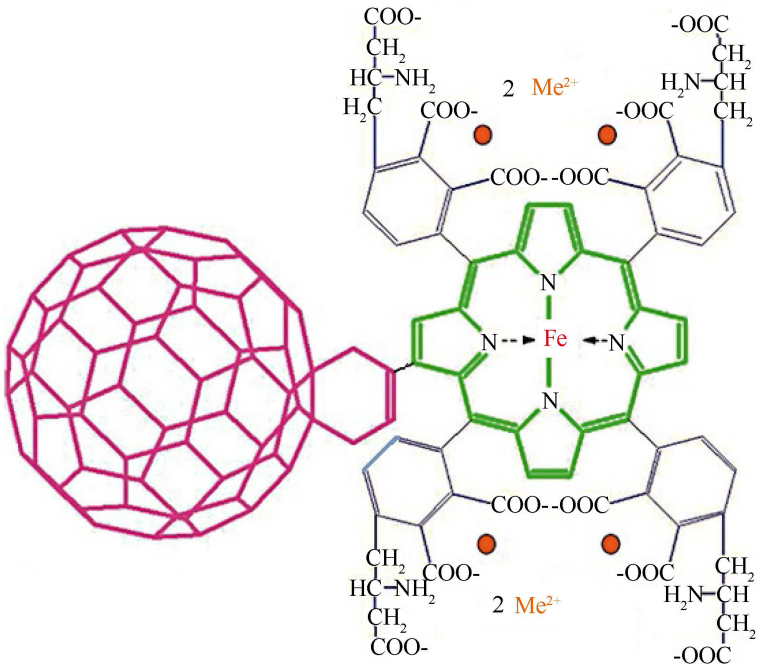

Figure 3. The structure of a PMC16 nanoparticle carrying $^{25}Mg^{2+}$cation [72].

Thus, nanocationites based on porphyrin-fullerenes (PMC16, **Figure 3**) are used for targeted delivery of $^{25}Mg^{2+}$ into tumor cells for the inhibition of β-like DNA Polymerases [15]. Each of the particles is capable of simultaneously transporting up to 4 divalent cations. Porphyrin-binding signaling proteins of the outer mitochondrial membranes of myeloblasts, promyelocytes, and a number of other cells serve as cation receptors [80]. At the same time, the release of the transported cation from the nanocontainer occurs only under the conditions of metabolic acidosis, which is specific for tumor tissue. Such a method of delivery may be especially promising for the treatment of malignant tumor metastases [15] [81].

Taking into account the promising potential of the paramagnetic isotope of the magnesium cation as an inhibitor of β-like DNA Polymerases in malignant tumors, the possibility of its uncontrolled negative effect on numerous metalloenzymes, including those of healthy cells, should be evaluated. Estimating this probability, it should be noted that most of the known metal-containing eukaryotic enzymes involved in the processes of intermolecular phosphate transfer have structural features that do not allow them to realize the magnetic isotope effect and, therefore, exclude the participation of these enzymes in a chaotic non-selective response to the presence of $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$cations [15] [50] [51] [76] [77]. The possible explanation for this phenomenon is that, according to the nanotopology of their active sites, the distance between the electron donor (the oxygen atom of the transferred phosphate group) and its acceptor (the metal cat-

ion) exceeds the distance of 7 - 10 nm, critical for the Coulomb ultrafine induction of singlet-triplet conversion of ion-radical pairs [51] [77] [79]. Such enzymes, in contrast to *β*-like DNA Polymerases, cannot serve as targets for paramagnetic cytostatic cations. The list of similar enzymes incapable of participating in spin-selective catalysis is very large [15] [75] [79].

Thus, the small number and relative homogeneity of the enzymes subjected to the effects of the magnetic isotopes (such as *β*-like DNA Polymerases from leukemia and retinoblastoma cells) are among the factors determining the selectivity of these agents as cytostatic drugs [7] [11] [78].

3.5. The Ultrashort 2'-Deoxypolyribonucleotides as Inhibitors of *β*-Like DNA Polymerases

The aptamer-like ultra short (30 – 150 *n*) single-stranded DNA fragments were detected in the blood of many cancer patients [82] [83]. For instance, patients with retinoblastoma demonstrate ultrashort single-stranded polydeoxyribonucleotides consisting from 50 - 150 nucleotide residues in their blood, not detected in healthy donors [70]. Such ultrashort circulating ssDNA fragments can be released into the blood from tumor cells during the repair of their genome.

The polynucleotide chains consisting of 40 - 100 of 2'-deoxyribonucleotides residues demonstrate inhibitory properties towards *β*-like DNA Polymerases from the malignant tumor cells of HL-60, WERI-RB-1, and Y-79 at the concentration of 6 - 60 μg/ml in the medium [33] [62]. At the same time, a positive correlation was found between the strength of the inhibitory effect and the affinity of the enzyme to the ligand. Interestingly, the inhibitory effect strength relies on the length of ssDNA rather than on its nucleotide composition. The maximum inhibitory effect was established for polynucleotides consisting of 40 - 60 2'-deoxyribonucleotide residues [33] [44].

The inhibitory effect of short ssDNA chains is explained by their reversible binding to the active site of the enzyme via van der Waals interactions. This process is nonspecific, and the inhibitor binding efficiency directly depends on the length of the polynucleotide chain [44] [71].

The short polynucleotides were shown to inhibit the reparative DNA Polymerases (such as pol*β*), and do not affect the replicative ones [33].

Based on the inhibitory effect of short and ultrashort polynucleotide chains on *β*-like DNA Polymerases and the fact that ssDNA easily penetrates the intracellular compartments (nuclei and mitochondria) [54], they can be used in tumor chemotherapy [33] [43] [44] [62].

The antitumor effect of 2'-deoxypolyribonucleotides was established both in tumor cell cultures and in the experiments on animals with various tumors (B16 melanoma, lung carcinoma, and P388 lymphoid leukemia) [33]. However, the practical use of the short polynucleotides in oncology is limited by the difficulty of their injection into tumor tissue. At the same time, special nanocarriers have recently been proposed for their targeted delivery to a tumor [15] [33] [84] [85].

Also, the use of *L*-polydeoxyribonucleotides eliminates their destruction by nucleases, as they hydrolyze only those polydeoxyribonucleotides which consist of D-monomers. Moreover, polynucleotides consisting of *L*-2'-deoxyribonucleotides were shown to have a more pronounced inhibitory effect towards *β*-like DNA Polymerases in human acute myeloid leukemia cells [34] [44] [71].

4. Conclusions

1) The overexpression of *β*-like DNA Polymerases takes place in malignant tumor cells.

2) The inhibition of *β*-like DNA Polymerases results in antiproliferative and antitumor effects.

3) The stable paramagnetic isotope of magnesium (^{25}Mg) or other nuclear spin possessing divalent metals ($^{43}Ca^{2+}$ and $^{67}Zn^{2+}$) as well as the short single-stranded 2'-deoxypolyribonucleotides are no doubt the promising anticancer agents.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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