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Review Article
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Magnetic Control of the DNA Synthesis by Nuclear Magnetic Ions of Mg, Ca and Zn as a Powerful and Universal Means to Kill Cancer Cells

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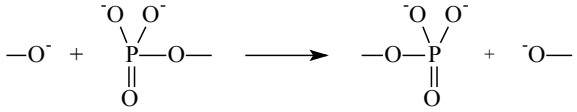
Abstract

DNA synthesis is commonly accepted to occur as a nucleophilic reaction catalyzed by Zn^{2+}, Ca^{2+} and Mg^{2+} ions. The substitution of these ions with nonmagnetic nuclei by ions with magnetic nuclei was shown to produce a huge isotope effect: magnetic ions suppress DNA synthesis by 3–5 times with respect to nonmagnetic ones. This observation unambiguously evidences that the DNA synthesis occurs by radical pair mechanism, which is well known in chemistry and implies pair wise generation of radicals by electron transfer between reaction partners. Magnetic field dependence of the DNA synthesis convincingly proves radical pair mechanism, which manifests itself even in the polymerase chain reaction. This mechanism, being on the energy scale by order of magnitude cheaper that the nucleophilic one, is switched on, when at least two ions enter into the catalytic site. It coexists with nucleophilic mechanism almost on a par; their competition is controlled by concentration of ions. Radical pair mechanism is induced by both sorts of ions, magnetic and nonmagnetic; the only difference is that it functions by 3-5 times more efficiently with magnetic ions. Nuclear magnetic ions $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$, decreasing catalytic activity of polymerase by 2-3 times, even more strongly, by 30-50 times, increase mortality of cancer cells. These ions may be considered as the cheap, easily available, safe (no influence on the immune, signaling and other protein systems), powerful, and universal anti-cancer means for selective killing cancer cells of any types.

Keywords: Magnetic isotope effect; DNA synthesis; Cancer cells

Introduction

Generally accepted mechanism of the DNA synthesis implies attachment of the nucleotide to the terminal ribose ring of the growing DNA, which occurs as a nucleophilic reaction. It implies that the reaction proceeds as an attack of phosphorus atom of the approaching nucleotide by ribose oxy-anion:



Enzymatic DNA synthesis is known to be catalyzed by Mg^{2+}, Ca^{2+}, and Zn^{2+} ions; they are traditionally considered to coordinate reactants in the catalytic site keeping them on the reaction trajectory to facilitate nucleophilic attack and probably slightly modify their reactivity due to partial redistribution of charges in the reactants. This nucleophilic paradigm excludes formation of any spin-carrying, paramagnetic intermediates and prevents radical mechanism of the DNA synthesis; no magnetic control of this reaction is supposed to be available. The discovery of magnetic isotope effect in chemistry [1-5] and biochemistry of the ATP synthesis [6,7] inspired to search the effect in enzymatic reactions. Indeed, the substitution of the catalyzing ions with nonmagnetic nuclei $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, and $^{64}Zn^{2+}$ by the ions with magnetic nuclei $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ was shown to produce a huge isotope effects: nuclear magnetic ions by 3–5 times suppress DNA synthesis with respect to nonmagnetic ions. This observation is unambiguous evidence that the DNA synthesis occurs by radical pair mechanism (RPM), which is known in chemistry [3-5] and implies pair wise generation of radicals by electron transfer between reaction partners. Evidently, this mechanism may be controlled by magnetic fields of isotopic nuclei as well as by external magnetic field. It is easy to guess that this unique phenomenon may have a medicinal application. The purpose of the paper is to elucidate molecular mechanism of the phenomenon, to describe conditions for its functioning, and to illustrate how it is used as a means to kill cancer cells.

Nuclear magnetic control of the DNA synthesis

Magnetic control of the polymerase β enzymatic activity in the DNA synthesis was detected by using pure isotopic ions of magnesium, zinc, and calcium, both magnetic and nonmagnetic, in catalytic sites. The activity was found to strongly depend on the nuclear magnetic moment: enzymatic activity of polymerases loaded with ions $^{25}Mg^{2+}$ with magnetic nuclei ^{25}Mg strongly (by 3-5 times) lower than the enzymatic activity of polymerases loaded with $^{24}Mg^{2+}$ and $^{26}Mg^{2+}$ ions carrying nonmagnetic nuclei ^{24}Mg and ^{26}Mg[7]. Polymerases with $^{24}Mg^{2+}$ and $^{26}Mg^{2+}$ ions exhibit no difference in enzymatic activity; it means that the mass-dependent isotope effect is ignorable. Similarly, isotopic ions $^{67}Zn^{2+}$ with magnetic nuclei ^{67}Zn strongly suppresses enzymatic activity of polymerase β (Figures 1 and 2). Almost identical effect is exhibited by polymerase β loaded with isotopic ions $^{40}Ca^{2+}$ and $^{43}Ca^{2+}$ (Figure 3). Like in the case of magnesium and zinc ions, $^{43}Ca^{2+}$ ions with magnetic nuclei ^{43}Ca strongly suppress enzymatic activity of polymerase with

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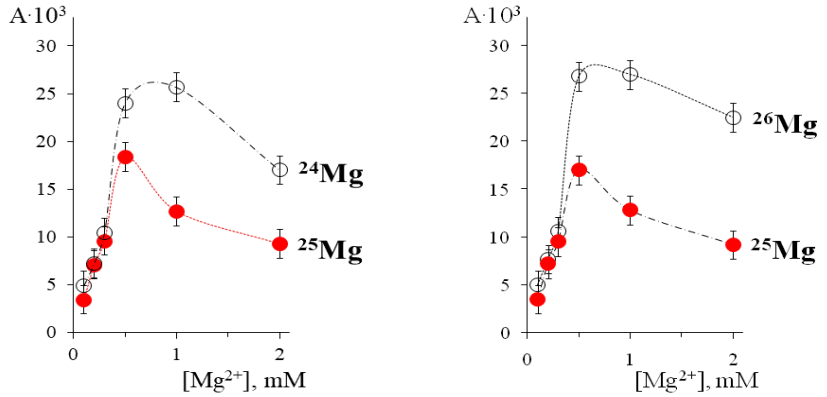


Figure 1: The rate of the DNA synthesis by polymerase β as a function of the low concentration the magnesium ions in pairs $^{24}Mg^{2+}/^{25}Mg^{2+}$ (A) and $^{26}Mg^{2+}/^{25}Mg^{2+}$ (B). Tritium radioactivity A is measured as the number of counts/min/mg of DNA. The content of ^{25}Mg, ^{24}Mg, and ^{26}Mg are 86.8%, 98.6%, and 98.4% respectively [7].

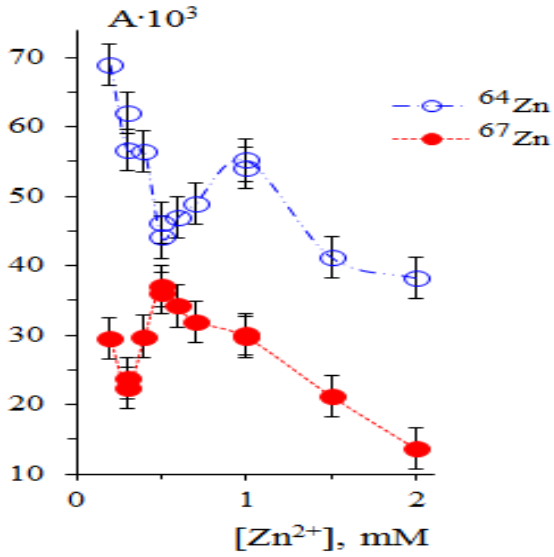


Figure 2: The rate of the DNA synthesis by polymerase β as a function of the zinc ion $^{64}Zn^{2+}/^{67}Zn^{2+}$ concentration.

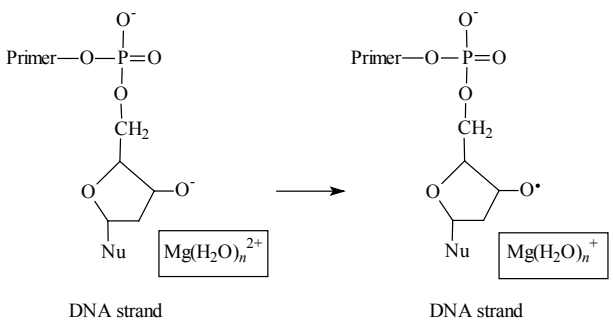
respect to polymerase loaded with nuclear nonmagnetic $^{40}Ca^{2+}$ ions [8,9].

Nuclear magnetic control of the polymerase chain reaction

It is remarkable that the extremely popular polymerase chain reaction (PCR) is also suppressed by $^{25}Mg^{2+}$ and $^{67}Zn^{2+}$ ions with magnetic nuclei ^{25}Mg and ^{67}Zn (Figure 4). Isotope effects on the rate of PCR-induced DNA synthesis and on the DNA synthesis induced by polymerase β are equal and demonstrate perfect similarity. Their activities are suppressed by $^{25}Mg^{2+}$ ions in an extent, which depends on the concentration of magnesium ions. At low concentration isotope effect is negligible but it increases as the concentration increases. This phenomenon seems to be universal for the DNA synthesizing enzymes; at least, it is valid for the two different enzymes, polymerase β and PCR-controlling polymerase. It is worth emphasizing that the observed magnetic effects have nothing to do with impurities or contaminations of reactants, they are intrinsic to the DNA synthesis itself [10].

Electron transfer as a source of radical pairs

Electron transfer as a source of the radical pairs is induced by remarkable property of enzymes to squeeze water molecules out of the catalytic site [11,12] when the enzyme domains are drawn together to unite reagents. The removal of water partly dehydrates catalyzing ions $M(H_2O)_n^{2+}$ (M is Mg, Zn, or Ca), increasing both positive charge on the core metal and electron affinity of the ion, so that at some threshold value n^* electron transfer becomes exoergic and energy allowed. The water molecule with number n^* in complex $M(H_2O)_n^{2+}$ functions as a trigger, it switches over the reaction between endoergic and exoergic regimes. At $n>n^*$ electron transfer is endoergic and energy forbidden, at $n<n^*$ it is exoergic and energy allowed. When n reaches n^* electron transfer becomes inevitable, switching on the radical pair mechanism. The idea of the RPM in enzymatic reactions was stemmed from the observation of magnetic effects; it was also supported by theoretical inspection. In the case of DNA synthesis electron is donated by ribose oxy-anion of the attaching nucleotide to the $M(H_2O)_n^{2+}$ ion (Scheme 1). The energy of this reaction was computed (Figures 5-7) to be negative for the large n, i.e., electron transfer is endothermic and forbidden in water. However, electron transfer is energy allowed even for the fully completed first hydrated sphere (n=6) of magnesium, zinc, and calcium ions [13,14]. Again, like in the case of the ATP synthesis, [15] the removal of water molecules by compression of the catalytic site in the DNA polymerases dehydrates catalyzing ions switching on energy cheap RPM. According to the RPM, the compression energy of enzymatic site is spent on the removal of water out of the ion hydrate



Scheme 1: Generation of the radical pair by electron transfer.

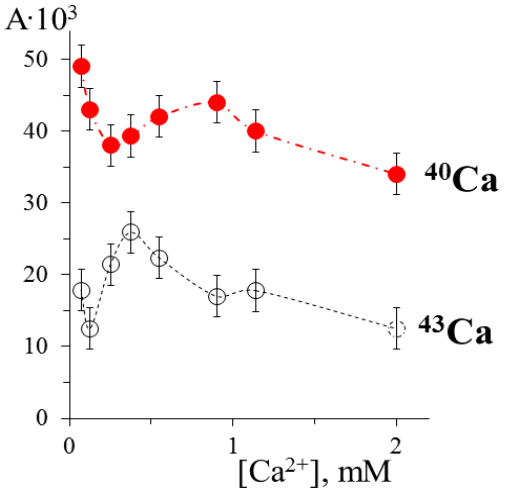


Figure 3: The rate of the DNA synthesis by polymerase β loaded with $^{40}Ca^{2+}$ and $^{43}Ca^{2+}$ as a function of the ion concentration [8].

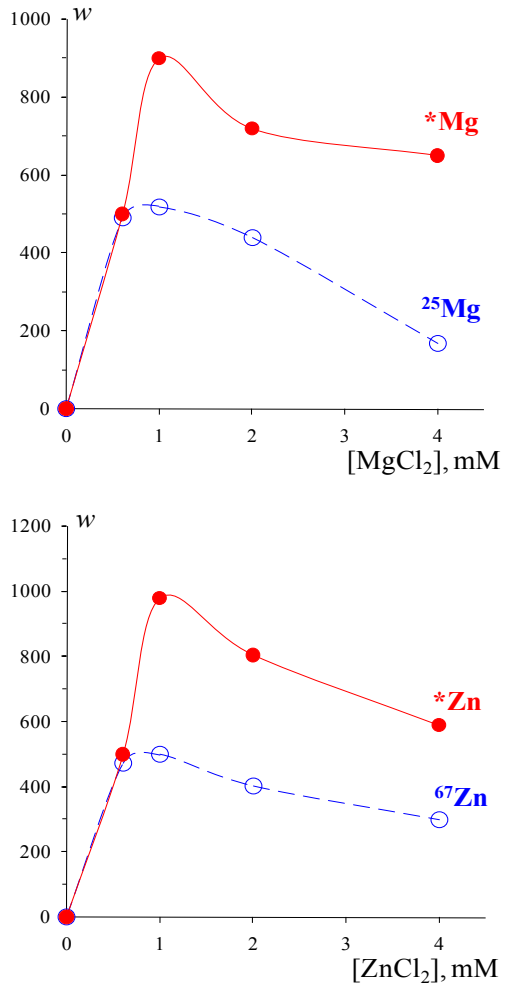
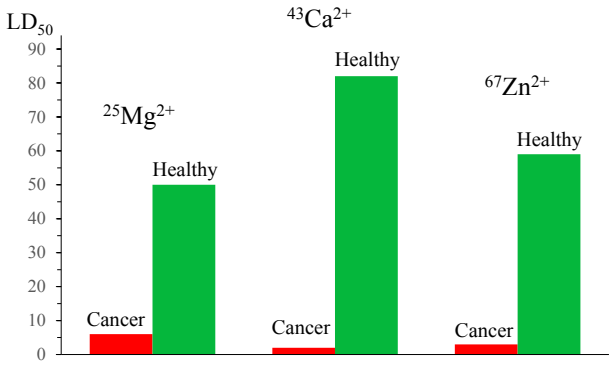


Figure 4: The yield of DNA ***w*** in the PCR-induced DNA synthesis with magnetic (^{25}Mg and ^{67}Zn) and nonmagnetic (*Mg and *Zn) ions as a function of the ion concentration [10].

shell, which activates this ion as an electron acceptor. In order to make electron transfer energy allowed it is enough to remove weakly bound water out of the external hydrate shells. In this process a total energy deficit does not exceed 3-5 kcal/mol, i.e., it takes almost by order of magnitude less energy than that required for the nucleophilic DNA synthesis. Being energy cheap (in contrast to energy expensive nucleophilic reaction) it is supposed to be switched on even at rather weak compression, i.e., electron transfer on the energy profile of the reaction should inevitably precede nucleophilic reaction. It implies that in terms of the RPM the M^{2+} ion is a central reactant, which functions reversibly and transforms mechanical energy of enzyme into the energy of the electron transfer, it is a key point, where molecular mechanics meets chemistry, where energy of conformational mechanics of the enzyme macromolecule transforms into the chemical energy. Of course, the details of the process cannot be certainly established but general idea seems to be worthy of confidence, otherwise it would not be possible to explain magnetic effects. In terms of commonly accepted two-magnesium-ion mechanism of the DNA synthesis [16-21] one of the ions is supposed to be tightly bound with pyrophosphate group of the incoming nucleotide and assists the departure of this group from the catalytic site after the insertion of the nucleotide into the growing DNA strand is completed. Another ion coordinates 3´O ribose ion of the DNA and P_α atom of the incoming nucleotide to facilitate nucleophilic in-line attack of 3´O on the P_α atom. In terms of the RPM namely this, almost free ion, is supposed to be an acceptor of electron; it generates radical pair by electron transfer from 3´O ribose ion to the $Mg(H_2O)_n^{2+}$ ion as a key, primary reaction (Scheme 2). The second step is an addition of the ribose oxy-radical to the P_α-O double bond of the incoming nucleotide. It generates a new oxy-radical OXY, which decomposes by β-scission mechanism along the three channels (Figure 6). Radical pair mechanism imitates nucleophilic one; the difference is that instead of one-step nucleophilic reaction (addition of 3´O• ion to the P_α atom of the incoming nucleotide, synchronized with release of pyrophosphate anion) the RPM implies three separate steps: electron transfer, addition of 3´O• radical to the incoming nucleotide phosphate generating new oxy-radical OXY, and decomposition of the latter along the three channels (Figure 6). Only channel 1 produces DNA but it is endoergic and not efficient. Channels 2 and 3 are exoergic and dominate but do not produce DNA. Ultimately, RPM appears to be strongly destructive and almost prevents DNA synthesis.

Coexistence of nucleophylic and radical pair mechanisms

Now we will discuss the concentration dependence of the nuclear magnetic effect, which, as mentioned above, is a key to the new mechanism of the DNA synthesis. At first sight these dependences



Scheme 2: Nuclear magnetic ions kill cancer cells.

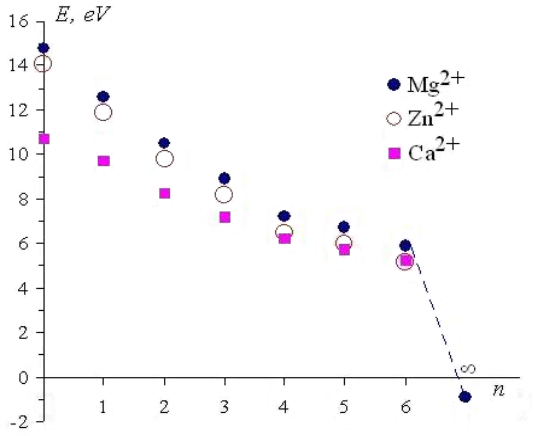


Figure 5: Energy of the electron transfer as a function of *n*, the number of water molecules in $M(H_2O)_n^{2+}$ ions [10].

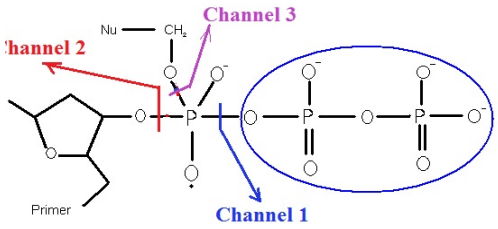


Figure 6: Three channels for the decay of the OXY radical.

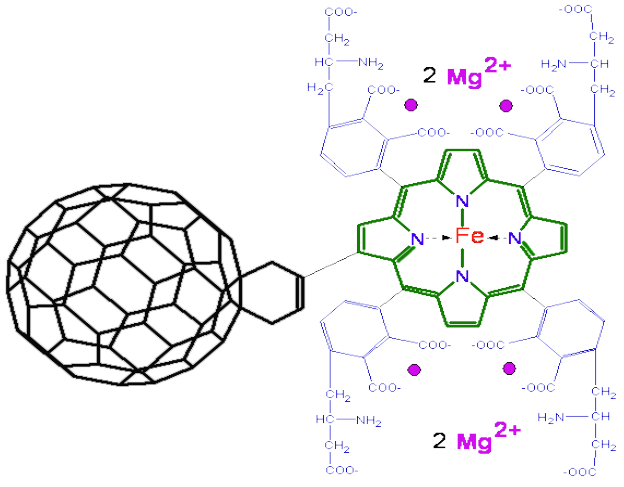


Figure 7: Nano-container PMC_{16} for delivering metal ions into the cells.

(Figures 1-4) seem to be enigmatic but they disclose new very delicate chemical features of the reaction. At low concentration of ions, ≤ 0.3 mM, the yield of DNA almost linearly increases as the concentration increases; no isotope effect exists. Two important conclusions follow from this observation. First, at these concentrations DNA synthesis occurs by nucleophilic mechanism, no electron transfer takes place, no isotope effect exists. Second, the presence of even a single ion in catalytic site is enough to induce nucleophilic mechanism. The number of sites loaded with the single ions increases as ion concentration increases; the latter results to linear growth of the DNA yield (Figure 3). When two ions appear in the catalytic site (at the concentrations ≥ 0.3 mM) electron transfer and RPM are switched on; as a result the rate of DNA synthesis decreases both in sites loaded with magnetic and nonmagnetic ions. Again two conclusions follow from this observation. First, both mechanism, nucleophilic and RPM, coexist at least on a par at these concentrations of ions; second, DNA synthesis is suppressed by RPM even in sites with nonmagnetic ions but magnetic ions suppress it by 2-3 times more efficiently. Magnetic effects are reliable, the most versatile tools and unambiguous indicators of the reaction mechanisms; their observation is an irrefutable argument in favor of the radical pair mechanism. It is also firmly supported by magnetic field effects.[10] However, inverted statement is invalid: if magnetic effects are not exhibited it does not mean that the radical pair mechanism does not function. There are three factors, which prevent detection of the magnetic effects even if the RPM is certainly known to function; they are discussed in the reviews [5,15]. As Jones pointed out, the absence of observed magnetic effects is not diagnostic of an absence of radical pairs and RPM [22,23]. As was pointed out in the Introduction, the radical pair mechanism is by almost order of magnitude cheaper in energy than the nucleophilic one. The discouraging questions arise, why RPM does not kill nucleophilic mechanism, why it does not prevent DNA synthesis completely, why both mechanisms coexist almost on a par. The reason seems to be in competition between the rates of the two processes: dynamics of the compressive motion and kinetics of ion dehydration. The fast motion of enzymatic protein domains ensures a regime, in which nucleophilic mechanism dominates. In the opposite case of slow motion the release of water molecules from the catalytic site and dehydration of metal ions have enough time to occur; then the RPM dominates. The balance of these two processes controls relative contributions of both mechanisms. It is evident that in living cells the balance depends mostly on the ion concentration. It is very possible that the RPM may operate in other polymerases, which accomplish replication of DNA and RNA; their molecular dynamics may control relative contributions of both mechanisms. It seems to be intriguing problem to disclose some unknown properties of these enzymes by studying their functioning at different concentrations of ions, both nuclear magnetic and nonmagnetic.

Does DNA polymerase need to capture the third Mg^{2+} ions to synthesize DNA?

Recently in the remarkable paper by Gao and Yang [24] the generally accepted two-magnesium-ion mechanism was revised; by using an elegant time-resolved technique of x-ray crystallography it was shown that the capture of the third Mg^{2+} ion is required for the DNA synthesis to occur. This conclusion seems to be highly likely valid for the reaction in crystallo catalysis, i.e., at the condition when the escape of the pyrophosphate ion as a reaction product, is strongly restricted in confined space of assembled complex. In native cell's DNA synthesis is hardly needs to be assisted by the third ion, which seems to facilitate departure of pyrophosphate ion. The similar effect of the third metal ion, coordinated by the reaction products, has also been observed in the polβ induced DNA synthesis, but only in crystallo catalysis [25-29]. Nevertheless, the function of the third ion remains to be enigmatic, particularly in terms of irregular dependences of the DNA yield on the ion concentration (Figures 1-4).

Anti-cancer effects

In contrast to the uncontrolled nucleophilic DNA synthesis radical

pair mechanism has a great advantage: it can be switched on artificially by delivering in cells some excess of magnetic or nonmagnetic catalyzing ions. For these specific purposes a metal ion carrier. based on porphyrin derivative of fullerene (Figure 7) has been designed [30-32]. First time it was successfully used for the targeted delivery of Mg^{2+} into the heart muscle [32]. These smart "nano-containers PMC16 release Mg^{2+} ions only in response to the metabolic acidosis, i.e., to the acidic pH shift known as a direct and inevitable consequence of a tissue hypoxia, but take them back once the normal cell metabolism restores. Nuclear magnetic ions $^{25}Mg^{2+}$, $^{67}Zn^{2+}$, and $^{43}Ca^{2+}$ were tested as a means to kill cancer cells HL-60. The ions were delivered into the cells by nano-container PMC16. Experimental magnitudes of LD_{50} for these molecules, loaded with the ions, were measured to be strongly different for the cancer and healthy cells (Figure 8). These results unambiguously demonstrate different survival of both sorts of cells; they show that cancer cells are much more vulnerable with respect to nuclear magnetic ions than the healthy cells. The effect is caused by the two reasons: first, mainly by nuclear magnetic field, which suppresses enzymatic activity of polymerases; second, by dominating selectivity of cancer cells, having probably more receptors to the nano-container than the healthy cells. Evidently, this medical aspect of the radical pair mechanism is extremely promising, particularly in preventing cancer metastases. Anti-cancer effect induced by nuclear-magnetic ions $^{43}Ca^{2+}$ was exhibited by polβ from HL-60 cancer cells [33]. The loading of these cells by $^{43}Ca^{2+}$ ions instead of $^{40}Ca^{2+}$ produced 2.25-fold inhibition of enzyme. Moreover, in regime of suppression a residual, low yield DNA synthesis produces short DNA fragments that count 25-35 nucleotides in length contrasting with the normal 180–210 nucleotides produced by $^{40}Ca^{2+}$ polymerase. These abnormally short, considered as "invalid" DNA segments are known to be inefficient in the DNA repair. These finding seems to be promising for cancer therapy and it is in a perfect agreement with the RPM mechanism of the DNA synthesis described in Sections 4 and 5. Indeed, the decomposition of OXY radical (Figure 6) terminates addition of nucleotides to the DNA chain and stops its growing. The remarkable anti-cancer effects were discovered by Bukhvostov et al. [34]. The activity A of pol β from the retinoblastoma cancer cells loaded with $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ ions is strongly, by 2.5-3.0 times, suppressed in comparison with that of cells loaded with $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, and $^{64}Zn^{2+}$ ions (Figure 9). The inhibition of DNA synthesis is accompanied by another effect, a sharp increasing the cell mortality: the CL_{50} values are significantly, by 10-12 times, less for the cells with $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ ions than for cells with $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, and $^{64}Zn^{2+}$ ions (Figure 10). Moreover, a shortening by 20-25% of the DNA fragments, processed with nuclear magnetic ions, is also occurred [34]. Catalytic activity of polβ isolated from the two sorts of human retinoblastoma cells, Y70 and WERI-RB, was shown to strongly depend on the nuclear spins of ions. At the identical conditions the polβ loaded with $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$ ions exhibited strong inhibitory effect for both sorts of cells decreasing the yield of DNA by 2-3 times with respect to ions $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, $^{64}Zn^{2+}$. The other benefit of nuclear magnetic ions is that they produce, like in the case of HL-60 cells, the short, "invalid" DNA segments inefficient for the DNA repair [35]. Nuclear spin-carrying isotopic ions $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$ were shown to promote the marked magnetic isotope effects on polymerase β in *ex vivo* survived human retinoblastoma cells; they promote the essential, by 2–3 times, inhibitory effect on the DNA synthesis in these cells (Figures 11 and 12) and lead to the sharp increase of cancer cell mortality [35,36]. It seems to be important to note general tendency that the radical pair mechanism functions only in the ATP and DNA synthesis, which are known to be accomplished by strong enzymatic molecular machines, however it does not work in phosphorylation of

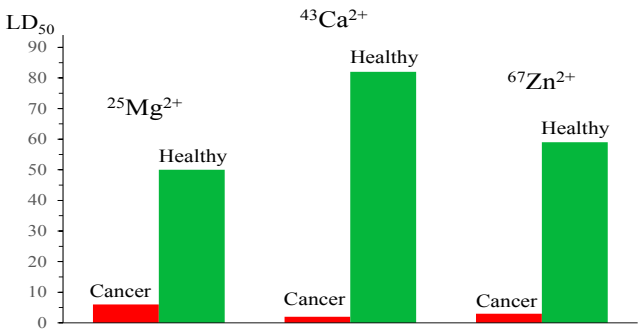


Figure 8: The LD_{50} of the nano-containers loaded with $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ ions for the cancer (red, left columns) and healthy (green, right columns) cells [33].

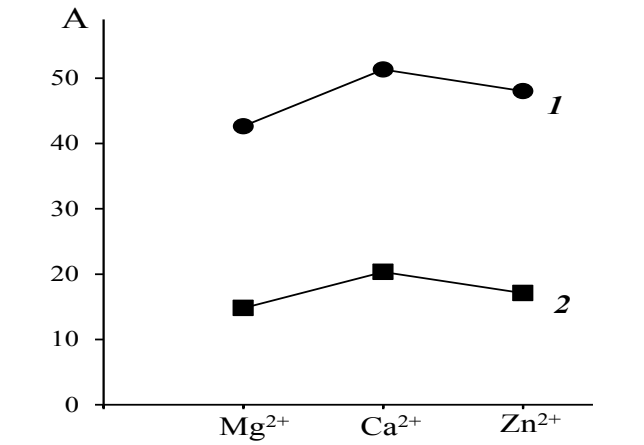


Figure 9: The activity A of pol β from the retinoblastoma cancer cells loaded with $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, $^{64}Zn^{2+}$ ions (***1***) and $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$ ions (***2***). The magnitudes of A are expressed in counts of tritium labeled DNA [34].

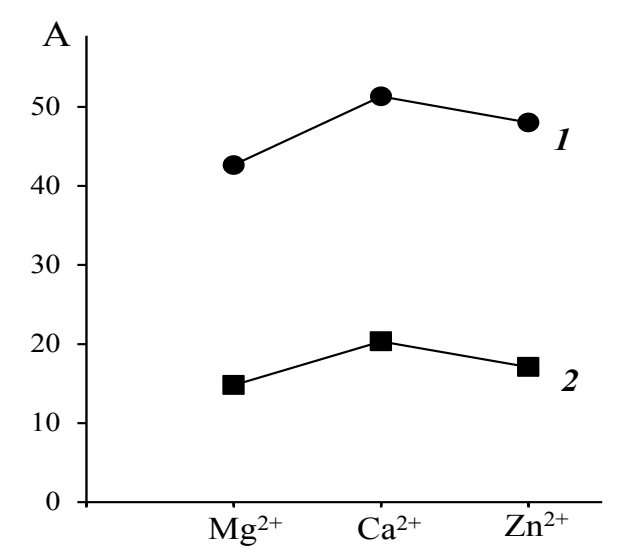


Figure 10: The LD_{50} of the $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, $^{64}Zn^{2+}$ ions (***1***) and $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$ ions (***2***) for the retinoblastoma cancer cells [34].

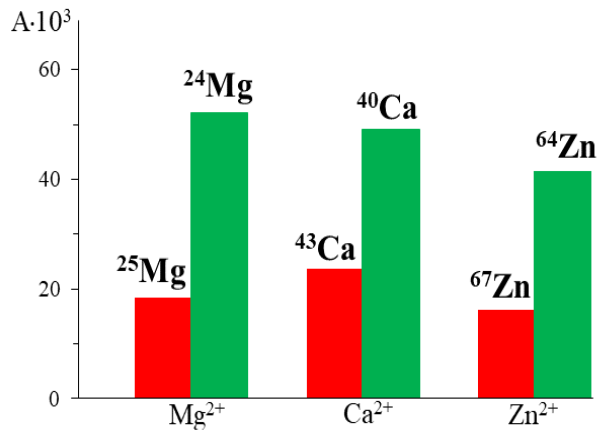


Figure 11: The activity A of pol β from the retinoblastoma cancer cells loaded with $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, $^{64}Zn^{2+}$ ions (green columns) and $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$ ions (red columns). The magnitudes of A are expressed in counts of tritium labeled DNA [36].

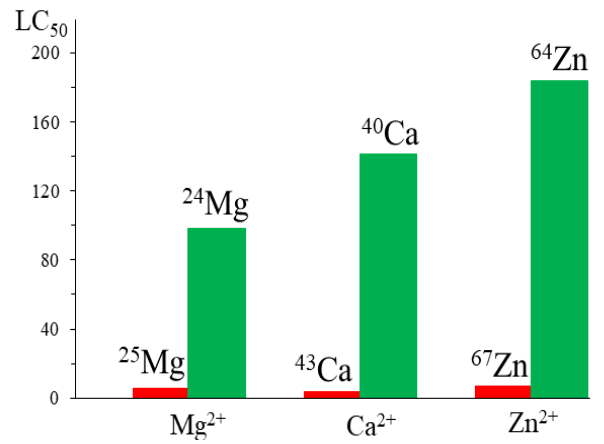


Figure 12: The LD_{50} magnitudes for the retinoblastoma cancer cells loaded with magnetic (red columns) and nonmagnetic (green columns) ions Mg^{2+}, Ca^{2+}, and Zn^{2+} [36].

proteins. It was demonstrated by example of prothrombin [33], which exhibits magnetic [25] Mg isotope effect only at very high (≥ 150 mM) concentrations; the latter are never reached in living organisms. The death of cancer cells occurs at much lower concentration, about 1 mM and even less (Figures 1-4). It means that nuclear magnetic ions are safe for immune, signaling and other protein systems subjected to phosphorylation. The extreme vulnerability of cancer cells to the ions with magnetic nuclei can be attributed neither to the possible difference in penetrability of membranes in cancer and healthy cells, since the isotope effect on the diffusion of ions through membranes should be certainly ignored, nor to the possible difference of ion concentrations in cancer and healthy cells. It cannot be also related to the functioning of polymerases with single- and double-stranded DNA, because in cancer and healthy cells DNA molecules are double-stranded and need unwinding by helicases. It is likely that the high mortality of cancer cells may be attributed to the specific function and high activity of polymerases in cancer cells. Nevertheless, it is necessary to admit that the firmly established large difference in the efficiency of magnetic ions to suppress DNA synthesis by 2-5 times with isolated polymerases and by 40-50 times in cancer cells remains intriguing and evidences that nuclear magnetic ions suppress not only polymerases but also another enzymes, which stimulate proliferation in cancer cells.

Conclusion

Both isotope and magnetic field effects reliably certify that in the DNA synthesis a new, radical pair mechanism functions, coexisting with generally accepted nucleophilic one. The heart of this mechanism is a radical pair, the two-spin nanoreactor. This mechanism seems to be universal; at least it functions identically in the two different enzymes, polymerase β and polymerase controlling PCR. It is worthy to note that the discovery of magnetic effects on the DNA synthesis simultaneously proves nucleophilic mechanism. Indeed, at low concentrations of metal ions there are no magnetic effects, i.e., nucleophilic mechanism dominates; at the concentrations ≥ 0.5 mM the RPM is switched on, which is accompanied by magnetic effects. Nuclear magnetic ions $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, $^{67}Zn^{2+}$ may be considered as a powerful and universal means to kill cancer cells, as the peculiar antibiotics, which induce their death.

Acknowledgments

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