Optical Control of DNA Base Radio Sensitivity

Ramin M. Abolfath†

Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas 75390

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We describe manipulation of the radio sensitivity of the nucleotide base driven by the spin blockade mechanism of diffusive free radicals against ionizing radiation. We theoretically propose a mechanism which uses the simultaneous application of circularly polarized light and an external magnetic field to control the polarization of the free radicals and create $S = 1$ electron−hole spin excitations (excitons) on a nucleotide base. We deploy an ab initio molecular dynamics model to calculate the characteristic parameters of the light needed for optical transitions. As a specific example, we present the numerical results calculated for a guanine in the presence of an OH free radical. To increase the radio resistivity of this system, an energy gap for the optical pumping and induction of excitons on guanine is predicted. The effect of spin injection on the formation of a free energy barrier in diffusion-controlled chemical reaction pathways leads to the control of radiation-induced base damage. The proposed method allows us to manipulate and partially suppress the damage induced by ionizing radiation.

Introduction

It is now well established that the interaction of ionizing radiation[1] with biological systems, e.g., DNA in the cell, occurs throughout a dynamical cascade of microscopic events and complex chemical pathways. The ionization or excitation of the DNA molecules, either directly or indirectly, can lead to DNA single- or double-strand breaks. In indirect mechanisms, the water molecules surrounding the DNA molecules that compose 80% of a cell may be excited by ionizing radiation in the form of free radicals, e.g., a hydroxyl radical (OH). The motion of charged neutral OH radicals which are randomly produced throughout the cell with a nanosecond lifetime is governed by the diffusion processes. Massive DNA damage can result from a large number of DNA dehydrogenations caused by OH radicals. For example, an OH radical that is within 1 nm from the surface of DNA molecule can diffuse and remove a hydrogen ion from it to form a water molecule. As a result, misrepaired DNA molecules can lead to specific genetic aberrations and/or mutations which could cause carcinogenesis in normal cells or lead to fatal damage in normal or cancer cells.[2,3] Experimental and phenomenological studies in radiobiology and radiochemistry have suggested that low linear energy transfer (LET) of ionizing radiation creates approximately 1000 single-strand breaks (SSBs) and 40 double-strand breaks (DSBs) per gray (1Gy = 1 J/kg) in typical mammalian cells.[4−7] The level of DNA molecular base damage has been estimated to be around 2500 to 25 000 per gray in a cell, which is about 2.5−25 times the yield of sugar−phosphate-induced damage in the DNA backbone.[4,7] Due to the high level of complexity of the interaction of ionizing radiation with cells and DNA, multiscale modeling and computer simulation of the DNA damage and repair mechanism at the molecular level is extremely challenging. Nevertheless, such studies, even on the simplified models at the qualitative level, can be found useful in identifying novel mechanisms through which the radiation-induced DNA damage becomes minimized. Here, we introduce a method that allows protection of DNA bases in solution. In particular, we take advantage of the nanosecond lifetime of free radicals and propose a dynamical mechanism based on a nanosecond quantum manipulation of electronic and spin states of the DNA bases by optical means to block the diffusion-controlled OH radical damages. Practical usefulness of this method for DNA in cell requires further investigations.

Method

In this work, we apply a quantum physical description of molecular interactions to propose a mechanism that could allow the manipulation of DNA radiosensitivity. In particular, the Pauli exclusion principle,[8] which prevents two electrons with parallel spin form occupying a single spatial orbital, plays a major role and is used to magnetically manipulate the diffusion of hydroxyl radicals and the OH−DNA relative motion. It has been shown in studies in semiconductor physics and quantum optics that the Pauli exclusion principle can be used to rectify electrical currents passing through weakly coupled quantum dots[11] and to induce ferromagnetic ordering by photogenerated carriers in magnetic semiconductor heterostructures.[12]

A free radical carries an odd number of electrons with an unpaired spin in the outermost open shell. Due to the reduction of the exchange interaction, the pairing of opposite spin electrons in the open orbital of the free radical with an electron in a DNA molecule makes free radicals highly reactive. In the process of dehydrogenation of a DNA molecule by free radicals, an unpaired hole (a half-empty orbital) is transferred to the DNA. In the absence of spin−orbit coupling and hyperfine interaction, the spin of the transferred electron is conserved. The electronic ground state of DNA molecule is $S = 0$ spin singlet (in the absence of an external magnetic field). The OH radical which contains nine electrons is a doubly degenerate ground state with $S_z = \pm 1/2$, where we have conveniently taken the quantization axis along the z-axis.The degeneracy of the ground state can be lifted by applying a weak magnetic field which couples to the electron spin through the Zeeman interaction,[8] $E_Z = g\mu_B \vec{S}\cdot\vec{B}$. Here E_Z is the Zeeman energy, g is the electron g-factor ($g \approx$

† Phone: 214-645-8541. Fax: 214-645-7622. E-mail: Mohammad.Abolfath@UTSouthwestern.edu.

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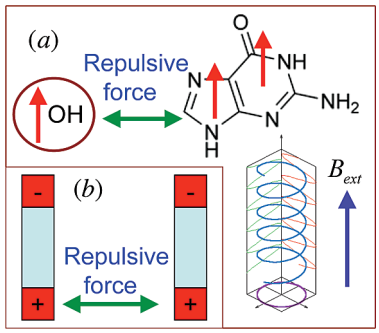

Figure 1. Schematically shown in (a) the injection of photogenerated electrons in DNA nucleotides with spin polarization (shown by arrows) along the direction of circularly polarized light and external magnetic field. The net magnetic force between two parallel magnetic moments localized in OH and DNA nucleotide is repulsive. This is similar to two separated magnetic moments which interact like a Heisenberg antiferromagnetic exchange coupling (b).

2), μ_B is the Bohr magneton ($\mu_B \approx 5.8 \times 10^{-5}$ eV/T), and B is the strength of external magnetic field.

In a random interaction of radiation with a biological system, the initial direction of OH radical magnetic moment immediately after its generation is also random. However, by applying a weak external magnetic field (B_{ext}) (which defines the quantization axis) and using a circularly polarized light field parallel to the direction of the light propagation, as shown in Figure 1a, a molecular transition corresponding to $\Delta J = \pm 1$ can be induced by means of optical pumping[13] of the OH radicals.[14] Here J denotes the total angular momentum of diatomic OH radical.[15] Alternatively, techniques such as electron spin resonance (ESR) can be used to achieve strong polarization of free radicals, as recent advances in ESR have demonstrated the capability of detecting the transfer of electron spin polarization between radicals.[9,10] In this case, microwaves can be used for the optical transitions. In a similar fashion, by applying a second circularly polarized light field, one may excite an electron−hole pair (exciton) in the DNA molecule. Because the circularly polarized light carries angular momentum ±1, the exciton has a particular spin polarization. We hypothetically assume that such terms such as spin-orbit coupling of the DNA electrons and/or the Zeeman coupling with external magnetic field allow direct/indirect optical spin-triplet transition. Here the spin of exciton is $S = 1$ with polarization along the light propagation direction (because of angular momentum selection rules). Figure 1 schematically shows the generation of the optically pumped exciton by circularly polarized light in the presence of external magnetic field. The injection of photoelectrons with the spin out of equilibrium may lead to a dramatic effect in the collective dynamical behavior of DNA molecules and the interaction with OH radicals. For example the OH−DNA repulsive magnetic force provides a potential barrier which blocks the diffusion pathway (see Figure 1b) of OH radicals toward the DNA molecules. This is expected to hinder the DNA dehydrogenation and consequently increase the cell radioresistivity. To verify this hypothesis, an ab initio molecular dynamical model, which is the mathematical formulation that governs the appropriate dynamics of the molecular system,[16] is deployed. We have used the Car−Parrinello molecular dynamics (CPMD)[18,19]model, in which the potential energy of the system can be calculated on the fly, as needed for the conformations of the dynamical trajectory to simulate the chemical reaction pathways. Because the absorption of a circularly polarized photon alters the local electronic state of a DNA molecule, we confine our simulation to a particular segment; e.g., only a part of the DNA where the injected exciton is localized and the optical transition takes place. To illustrate this, let us consider a system of interest consisting of a DNA nucleotide base, (e.g., guanine) in the presence of the OH radical. We assume that a photon with circular polarization interacting with guanine can induce an optical transition in the form of an $S = 1$ exciton. Here we investigate the effect of an exciton produced in this way on the guanine-dehydrogenation pathway, assuming that another photon generated through interactions with ionizing radiation (such as radiotherapy X-rays or cosmic rays) creates a free radical in the vicinity of guanine. Because the local density of free radicals and excitons are large and are comparable, the events described in our calculation is expected to be observed with reasonable probability. We adopt computational parameters and variables needed for the CPMD calculation of the dynamical trajectory of the gas-phase nucleotide bases in the presence of OH radicals following ref 17, where the consistency of CPMD results for guanine with other quantum chemistry approaches has been investigated.

Results

We identify the dehydrogenation of the nucleotide bases as a function of their spin multiplicity. The ground and excited states of the nucleotide correspond to spin singlet ($S = 0$), and spin triplet ($S = 1$) states. The latter can be realized through the application of circularly polarized light as discussed above (see Figure 1). Our CPMD is implemented in a plane-wave basis within local spin density approximation (LSDA) with an energy cutoff of 70 Ry (rydberg), and with Becke[20] exchange and Lee−Yang−Parr (BLYP) gradient-corrected functional.[21] Norm conserving ultrasoft Vanderbilt pseudopotentials were used for oxygen, hydrogen, nitrogen, and carbon. The CPMD microcanonical dynamics (constant energy ensemble) were performed after wave function optimization following dynamical equilibration at $T = 300$ K and requenching of the wave function. An isolated cubic cell of length 13.229 Å with Poisson solver of Martyna and Tuckerman[22] was used. Our CPMD studies consist of two classes of spin-restricted calculations, as the total spin along the quantum axis is subjected to the constraints $S_z = 1/2$ and 3/2, corresponding to doublet and quartet spin configurations. In both calculations, the initial distance between OH radical and nucleotide is considered to be about 1.5 Å. We selectively choose an initial coordinate for OH radical in the neighborhood of the nucleotide where the hydrogen transfer shows a reactive path in normal state of DNA (the doublet spin configuration in the absence of circularly polarized light and magnetic field).

The initial and final states of the molecules are shown in Figures 2−4. The final configurations of the molecules have been obtained after 0.6 ps where the rearrangement of the atomic coordinates have been deduced from a dynamical trajectory calculated by CPMD. According to our results, a rapid dehydrogenation of the nucleotides takes place for a system with $S_z = 1/2$ (spin doublet) as shown in Figure 3. This process leads to the formation of a water molecule. In contrast, as shown in Figure 4, in the quartet spin configuration the repulsive exchange interaction, analogous to Heisenberg antiferromagnetic coupling which originates from the Pauli exclusion principle, blocks the exchange of hydrogen and hence the chemical reaction. In Figure 5 the evolution of the N_1 hydrogen in the guanine and free radical oxygen distance is shown. As it is seen, the abstraction of hydrogen occurs around $t \approx 50$ fs in the spin singlet state of guanine, and the injection of $S = 1$ exciton in guanine blocks the hydrogen abstraction. Figure 6 shows the Kohn−Sham energies (equivalent to potential energy in classical

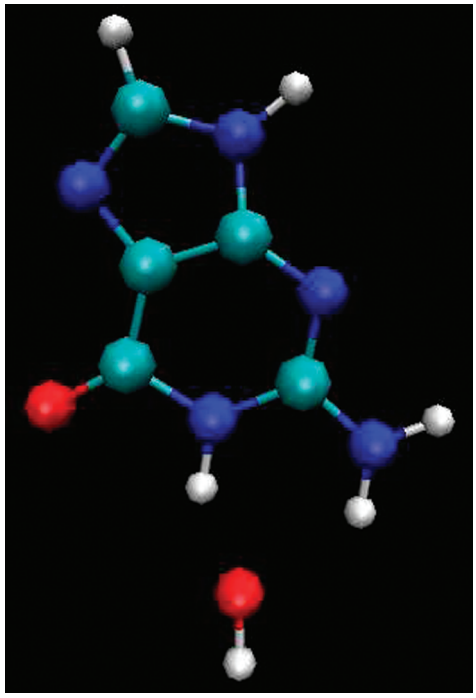

Figure 2. Initial state of guanine molecule in the presence of irradiated induced OH free radical.

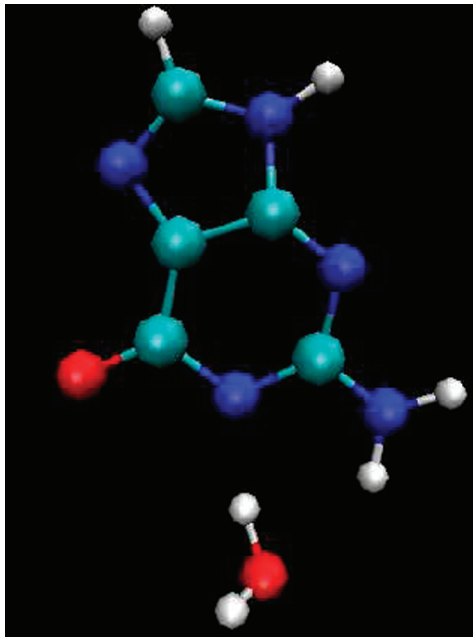

Figure 3. State of dehydrogenated guanine by OH free radical at $t =$ 0.6 ps. The polarization state of the system is spin doublet ($S_z = 1/2$).

molecular dynamics) of the spin singlet and spin triplet of the Guanine in the presence of the OH free radical as a function of time, calculated by the CPMD at $T = 300$ K corresponding to a canonical dynamics (constant temperature ensemble). A drop in Kohn−Sham energy in spin singlet multiplicity is indication of dehydrogenation of H_{N1} in the guanine by OH free radical. To systematically check the convergence of the results, we increased the size of the molecule by adding sugar−phosphate rings to guanine and found that this has no influence on the spin-blockade effect. To estimate the energy needed for the spin polarization of the nucleotide in the absence of OH radicals, we calculated the energy of the ground and excited states of

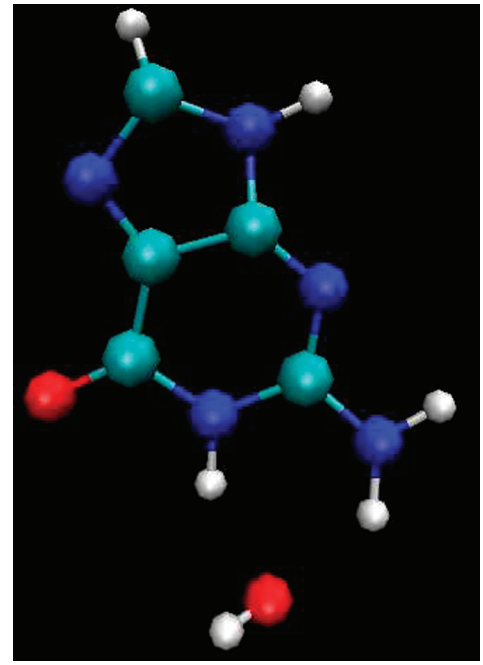

Figure 4. State of radioresistive guanine at $t = 0.6$ ps. The polarization state of the system is spin quartet ($S_z = 3/2$) induced by circularly polarized light in the presence of weak magnetic field. Due to injected polarized photoelectrons localized in guanine, the dehydrogenated guanine does not form.

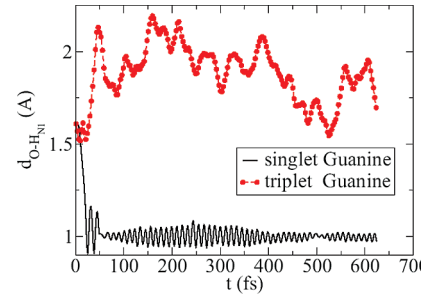

Figure 5. Evolution of the distances (in Å) from oxygen atom in the OH radical to the H_{N1} in the guanine as a function of guanine spin multiplicity. The hydrogen abstraction occurs around $t = 50$ fs in the spin singlet state of guanine. The injection of $S_z = 1$ exciton in guanine blocks the hydrogen abstraction.

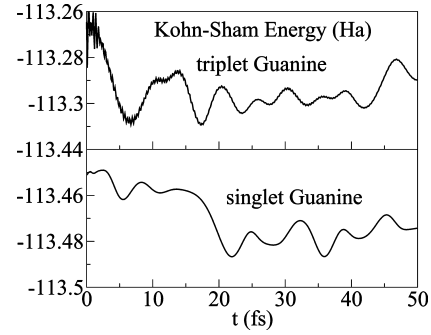

Figure 6. Kohn−Sham energy as a function of time and spin multiplicity of guanine, spin triplet (top) and spin singlet (bottom). A drop in Kohn−Sham energy in spin singlet multiplicity is indication of dehydrogenation of H_{N1} in the guanine by OH free radical.

the gas-phase nucleotide in spin singlet and triplet multiplicities. For guanine we calculated the spin singlet−spin triplet energy gap $\Delta_0 \equiv E_{\text{triplet}} - E_{\text{singlet}} \approx 2.68$ eV. This provides an estimate for the frequency of the circularly polarized light, which is within the range of the visible spectrum of the electromagnetic

waves, $\lambda = 463$ nm (light blue). To calculate the stored magnetic energy due to the optical injection of spin, we calculated the energy of the gas-phase nucleotide in the presence of one OH free radical with spin doublet and quartet multiplicities. For the molecules shown in Figure 2, we find the energy gap $\Delta_0 \equiv E_{\text{quartet}} - E_{\text{doublet}} \approx 3.54$ eV. Here, the excessive magnetic energy which originated from spin−spin repulsive interactions (which resemble the antiferromagnetic exchange interaction in the Heisenberg model) can be deduced to be $\Delta_1 - \Delta_0 \approx 0.86$ eV. This energy can be interpreted as the excessive energy barrier due to the alignment of the spins in the DNA molecule and OH and is the source of the magnetic repulsive force which makes the diffusion of OH toward DNA molecules less likely. This is in agreement with the results obtained from CPMD, shown in Figures 2−4. In addition, by switching the polarization of one of the light sources to the opposite direction, the relative direction of the DNA−OH polarization switches to antiparallel, and hence the magnetic repulsive force changes to an attractive force that lowers the OH diffusion barrier and decreases the radiosensitivity of the DNA molecule.

After photon absorption, the nucleotide is spin polarized along the direction determined by the polarization state and the propagation direction of the circularly polarized light. The polarized state of the nucleotide then decays quantum mechanically to its unpolarized ground-state either by spontaneous photon emission (electron−hole recombination) or through photon-electron spin decoherence. There are radiative and nonradiative channels that contribute to this process. Since spin−orbit coupling governs one of the decay mechanisms we use Fermi's golden rule to estimate the lifetime of the triplet state. It then follows that $\Gamma_{T\to S} = (2\pi)/(\hbar^2)\ \Omega\int d^3k/(2\pi)^3|\langle T|H_{SO}|S\rangle|^2\delta(\omega_0 - \omega)$.[8] Here $\Gamma_{T\to S}$ is the transition rate from the spin-triplet (T) to the spin-singlet (S) state, Ω is the volume, $k = 2\pi/\lambda$ is the emitted photon wavenumber, $H_{SO} = (-e)/(2m^2c^2)\sum_{i=1}^{N} \vec{S}_i\cdot(\vec{p}_i \times \vec{\nabla}\Phi_{KS}(\vec{r}_i))$ is the spin−orbit Hamiltonian, m is the electron mass, c is the speed of light, S_i and p_i are the spin and momentum of the ith electron, Φ_{KS} is the Kohn−Sham effective potential, and $\omega_0 = \Delta_0/\hbar$. This calculation shows that $\tau = \Gamma_{T\to S}^{-1} \approx 100$ ps. However, the electronic relaxed excitonic states with empirical lifetime of several 100 ps has been reported recently.[23] The spin-triplet lifetime of nucleotide τ turns out to be significantly larger than the dehydrogenation time scale. It is therefore possible to increase the radioresistivity of the DNA molecule within this time scale through optically pumped spin polarization. It is important to compare τ with other time-scales in the process. The initial ionization takes place in about 1 fs (10^{-15} s). The primary free radicals produced by ejection of electrons have a lifetime of nearly 100 ps, and the reported OH radical lifetime is about 1 ns (10^{-9} s).[3] The electron spin−lattice relaxation time of the OH radical has been estimated to be approximately between 0.1 and 0.5 ns in water at room temperature.[10]

In order to estimate the technical requirements for the above-described approach, one could assume that an aqueous solution of DNA will be irradiated with a dose of 1 gray. It is known[24] that 100 eV of absorbed photon/electron energy produces about 6 OH radicals. Therefore, 1Gy of radiation produce about 4×10^{13} OH radicals in 0.1 cm^{-3} of water. If the number of injected excitons can be exceeded up to at least 10 times, by applying a laser pump with moderate intensity it is possible to increase significantly the resistance of DNA molecules against irradiation. For example, at a dose rate of 1.4 gray/min a laser pump power of $P = 10N_{OH}(\hbar\omega_0)/\tau_{irr} \approx 12 \times 10^{-6}$ W would be required, which is well within the technically achievable limits.

Conclusion

In conclusion, we have theoretically explored a mechanism which involves the injection of spin-polarized excitons in DNA molecules to control and manipulate the radiosensitivity of cells by using a circularly polarized light field and external magnetic field. The mechanism proposed here is based on the selection rules applicable to optical transitions between energy levels of the DNA molecules and optical pumping of the OH radicals, and we have employed a microscopic ab initio molecular dynamics model to computationally study the dehydrogenation mechanism at the molecular level. The results of this study may be used as a guideline to develop new techniques for radiation therapy and radiation protection purposes.

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