Low-energy electron Damage to DNA

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The complex physical and chemical reactions between the large number of low-energy (0-30 eV) electrons (LEEs) released by high energy radiation interacting with genetic material can lead to the formation of various DNA lesions such as single strand breaks (SSBs), crosslinks (CLs), base modifications, double strand breaks (DSBs) and other clustered lesions.

Keywords: DNA damage ; low-energy electrons ; transient anions ; dissociative electron attachment ; radiotherapy

1. Introduction

The damage induced to living organisms by high energy radiation (HER) is usually seen as occurring via a sequence of events, which can modify the irradiated cells and their behavior. These events can be broadly divided into physical, physico-chemical, chemical, and biological stages [1]. In the latter stage, the cell responds to the chemical transformations induced by the radiation. Except for neutron irradiation, during the physical stage, primary ionizations and excitations result from the propagation within biological tissue of charged energetic particles (i.e., fast electrons, protons, or ions) or fast electrons produced by primary high energy photons [2]. Most of the energy of these fast particles flows into the production of a large number (~4 × 10 4 per MeV of deposited energy) of cations and secondary electrons (SEs). It is for this reason that SEs carry most of the energy deposited in cells by HER. SEs have energies ranging from zero to several hundreds of eV. The large majority produced below 20 eV is designated as low-energy electrons (LEEs). The most probable energy of SEs lies around 9–10 eV [3].

During the physico-chemical stage, cations and SEs recombine or react within femtoseconds, with molecules or subunits of large biomolecules in radiation tracks [4]. Both species produce excited states and radicals, but SEs can produce further ionization and transient anions (TAs). Dissociation of a TA result in the formation of a neutral radical and an anion (i.e., dissociative electron attachment; DEA) [5][6]. Alternatively, autodetachment of an extra electron from a TA can leave the molecule or molecular subunit in a vibrational or electronic excited state [7]. Dissociative electronically excited states resulting from both primary particle or SE interactions can lead to the creation of energetic ions and radicals [8][9][10]. When these species react with surrounding biomolecules before being thermalized; the phenomenon is referred to as “reactive scattering”. Both the latter type of reactions and electron-hole (cation) recombination are included in the physico-chemical stage [2][9][11]. Once the radicals, atoms, and new products induced by the radiation have thermalized, diffusion-controlled reactions occur as the irradiated system enters the chemical stage. At the end of this stage, the biological response is initiated, during which toxic products are eliminated and the damage is usually repaired. If not, mutation, necrosis or apoptosis can occur.

However, it has recently been shown that the initial capture of a single electron by a base, leading to TA formation within DNA, can directly cause potentially lethal cluster lesions, thus by-passing the chemical stage [12]. In other words, the well-established sequence of events is not necessarily followed in the case of TAs, since their decay followed by electron transfer within DNA can produce CLs and cluster lesions, as explained later in the text with Scheme 1 . This is a single-hit mechanism that does not depend on the density of DNA damages, as in the case of cluster damages caused by multiple hits [13][14]. This TA mechanism does not rely on linear energy transfer (LET), as the ensuing cluster yields are linearly proportional to the number of LEEs along HER tracks [15]. When multiple events become effective in causing cluster lesions at high LET, the TA mechanism is still present, and its effects must be added to those created by multiple events [12]. The TA mechanism is different than the accepted mechanism leading to cluster lesions, which derives from random multiple hits by radiation-generated species along tracks that can cause two or more simple lesions, within one or two turns of the DNA helix [13][14][15][16]. Both a single LEE and multiple hits can produce a potentially lethal lesion within DNA during the initial (i.e., non-thermal) energy deposition process and hence bypass the chemical stage. These notions are particularly important to understand the radiobiological effectiveness of HER, which relates particle and photon irradiation

to biological outcome [17]. Thus, understanding LEE-induced processes in DNA has implications, not only in the description of the physico-chemical stage of energy deposition, but also in explaining the production of DNA lesions potentially lethal to cells during the initial energy deposition process [12][18].

2. Mechanisms of Action of LEEs and Induced DNA Damage

The dynamics of LEE scattering in a dilute gas or within condensed material must be described in terms of wave functions. For a given situation and electron energy, the associated wave function can be expanded into a superposition of simpler plane waves. Intra- as well as inter-molecular interferences of such waves play a dominant role in LEE scattering within condensed matter. The scattering of LEEs from condensed atoms or molecule generates wave functions of wavelengths comparable to the size of molecules and the distances between them in biological media. In large biomolecules, LEE wavelengths are commensurate with the distances between the constituent fundamental units or molecular building blocks. Hence, intra- and inter-molecular coherent scattering modulate electron energy losses and molecular dissociations via localized (e.g., vibrational and electronic excitation) [19][20] and delocalized processes [21][22], including phonon [23][24] and exciton [25] creation and charge transfer [26][27]. Even in cells, where the random orientation of biomolecules and fast energy loss events can destroy long-range coherence, constructive interference of electron waves is still expected to persist, as shown in amorphous ice [28]. Furthermore, Caron and Sanche [29] demonstrated that the formation and decay of TAs are influenced by diffraction of LEEs within the DNA molecules. As a general rule, when disorder between condensed molecules increases, long-range coherent scattering of the electron waves arising from orderly positioned molecules diminishes and intra-molecular scattering phenomena become more dominant [30][31][32]. Hence, description of scattering processes in terms of the mechanisms of isolated electron–molecule interactions remain valid. However, these processes are modified by the presence of other neighboring targets and the band structure of the solid or liquid [5][29][33].

The formation of TAs and their decay channels have been amply described and reviewed in the literature [5][6][11][34][35][31]. The perturbating effects of water on TA formation and decay has also been reviewed recently with emphasis on theoretical progress [36]. A TA state has an intrinsic width in energy that depends on its lifetime. The resonance width can be determined from the dependence on electron energy of elastic scattering, a particular energy-loss process or product yields. There are two major types of TAs [5][34]: shape and core-excited resonances. Single-particle or shape resonances occur when the attaching electron occupies an otherwise unfilled orbital of the target molecule in its ground state. Such an electron capture can also occur at the site of a fundamental or subunit of a large biomolecule, such as DNA [34][37]. Core-excited resonances or ‘two-particle, one-hole’ states result from electron capture by the positive electron affinity of an excited state of the target molecule, or fundamental subunit of a large biomolecule, such as a base, sugar, or phosphate group in the DNA molecule. A core-excited anion can re-emit the electron (i.e., autoionization) into the scattering continuum or another site of a large molecule [33], leaving the target in the ground state or in excited rotational, intramolecular, and intermolecular (i.e., phonon) vibrational modes, as well as in electronically excited states. Dipole-bound electron resonances constitute another category of TAs that can lead to fragmentation or electron stabilization [38][39][40][41]. In this case, beyond a critical value of the dipole moment, the electron is captured by the long-range dipole potential of a target molecule. However, the electron-dipole interaction extends beyond the distances between molecules in condensed matter [38][39]. Dipole-bound anion are therefore not expected to exist in that phase, because of the overlap of the electron-molecule potentials of neighboring molecules [29]. In the case of water clusters for example, up to about 10–12 water molecules, the excess electron remains in the dipole potential [40]. Otherwise, water molecules form one or more complete hydration shells, causing the additional electron to migrate into an orbital localized on the outer surface of the water cage [40]. Related results are mentioned in Section 6 of the present article.

Below about 15 eV, electrons can temporarily attach at specific energies to DNA and its fundamental subunits [37][42]. In short oligonucleotides, the incoming LEE can be captured, with similar probabilities, by the phosphate group or by a base [37][42]. In long duplex DNA or plasmids, electrons with energies below 15 eV are mostly captured by a base, forming a TA of that base [43][44]. Below 4 eV, only shape resonances can locate an electron in an otherwise unfilled orbital of a base since electronic excitation is not energetically possible. Martin et al. reported the presence of two maxima at 0.8 and 2.2 eV in the electron-energy dependence of the yields (i.e., the yield function) of SSBs in plasmid DNA [45]. These enhancements were interpreted as shape resonances, resulting from electron attachment into the otherwise empty π* valence molecular orbitals of the DNA bases [46]. Dissociation of the base TA can produce an abasic site or a base damage (BD) [43][42]. As predicted theoretically, SSBs can also occur due to electron transfer from this π* orbital to a low-lying σ* orbital of the phosphate group, forming a dissociative TA at that site [37][46]. At higher energies up to about 15 eV, this type of process occurs via core-excited resonances, from which an electron can also transfer to the sugar-phosphate group [43][37][47][48]. Thus, over the entire 0–15 eV range, a TA formed on a base can dissociate via DEA producing an abasic site or a BD [43]. Moreover, an electron can autodetach from a base TA, while leaving the base in a dissociative

electronic excited state. The detaching electron can also transfer to another fundamental unit, where DEA can occur [43][37][44]. Thus, simultaneous base dissociation and electron transfer within DNA open channels for multiple damages induced by a single electron.

3. Conclusions

We now know that LEEs interact strongly with DNA via the formation of TAs and attach usually first to the DNA bases, with a preference for guanine in the range 0–4 eV. These TAs can decay by autoionization or DEA. The latter process can damage dry DNA over the entire 0 to 12 eV range, whereas autoionization can be destructive above the electronic excitation energy threshold. However, these decay channels are influenced by other relevant biomolecules surrounding DNA. According to theory and cluster experiments, below about 4 eV, the damage to small DNA constituents (e.g., the bases and nucleotides) is considerably suppressed, when they are surrounded by water molecules. This decrease in DEA has been attributed to a perturbation of the lifetime and change in the energy of the shape resonances below 4 eV. In particular, the upward energy shift of the curve-crossing of the extra-electron π and σ orbitals of the base and phosphate groups, respectively, considerably reduces electron transfer from the bases to the phosphate group and thus decreases the number of SSBs. Above this energy, the presence of water around single and double DNA strands increases damage yields. In long sequences of duplex DNA, bond scission occurs with or without intramolecular transfer of an electron detaching from a TA; such transfer usually occurs from a base to the phosphate group. From these processes, it was shown that within femtoseconds after their creation by ionization, LEEs can induce potentially lethal DNA lesions.

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