

The Role of Low Energy Electrons in Radiobiology and Cancer Treatment

Sasan Esmaili ^{1,*} , Farzaneh Allaveisi ²

¹ Department of Radiobiology and Nuclear Medicine, Faculty of Medical Sciences, University of Sherbrooke, QC, Canada

² Department of Medical Physics, Kurdistan University of Medical Sciences, Sanandaj, Iran

*Corresponding Author: Sasan Esmaili
Email: Sasan_esmaili@yahoo.com

Received: 16 December 2020 / Accepted: 25 December 2020

Abstract

Low energy radiation can be produced by all types of high energy radiation. Studies of low energy particle radiation help us to understand the chemistry induced by high energy radiations. Low energy electrons are capable of chemical selectivity in contrast to high energy electrons due to the large number of open dissociative channels in the former case and their resonant nature. Among different types of radiation, low energy electrons have a higher cross-section to DNA damage and they have an important role in the synergistic effect between radiation and chemotherapy anticancer agents in cancer treatment. Analysis of these combined records helps assign function of cells, identify metabolic and regulatory pathways and suggest targets for diagnostics and therapeutics identify animal models to develop new drugs, among other goals of biomedical interest.

Keywords: Cancer; Cross Section; DNA Damage; Low Energy Electrons.

1. Introduction

Excess deaths associated with COVID-19, the death rate from cancer is still growing. In 2020, there will be an estimated 1.8 million new cancer cases diagnosed and 606,520 cancer deaths in the United States [1]. There are several different approaches for cancer treatment, depending on the type of cancer, how advanced it is, what types of treatment are available, and what the goals of treatment are. Obviously, radiotherapy continues to serve as a primary cancer treatment modality; consequently, the development of strategies that improve its efficacy is likely to have an impact on a significant number of patients. Toward this end, radiation is typically combined with standard cytotoxic chemotherapeutic agents, an approach that has become the standard of care for a number of solid tumor types, including lung, head and neck, gastrointestinal, and brain tumors. The processes through which radio-chemotherapy could provide treatment benefits were initially put forth by Steel and Peckham in 1979 [2] and included concepts of spatial cooperation, toxicity independence, and enhanced tumor radio-sensitivity.

The vulnerability of cancer cells due to irradiation by ionizing radiation is the clinical rationale for the use of platinum-based Concurrent Chemo-Radiotherapy (CCRT) for cancer treatment [3]. Extensive efforts have thus been made in the past two decades towards experimental and theoretical studies of efficacy of CCRT [3-5]. The mechanisms of radio-sensitization and their respective contributions are still under debate [6]. However, inhibition of DNA repair and lethal DNA lesions such as Single Strand Breaks (SSB) and Double-Strand Breaks (DSB) may contribute to the efficacy of CCRT [7]. While DSB induced by ionizing radiations can disturb the DNA structure and triggering cell death, irradiation can also affect plasma membrane and subcellular organelles, and induce the activation of cell stress response-related genes and intracellular signaling pathways, triggering cell death. New research findings on radiochemistry in biological macromolecules such as DNA, suggested that the abundant near zero-eV (0.5 eV) electrons, created by high energy ionizing radiation during radiotherapy, induce DSB in supercoiled plasmid DNA modified by platinum-containing anticancer drugs (like Pt drugs), but not in unmodified DNA [8, 9]. This is a piece of evidence that shows these Low Energy Electrons (LEEs) are able to

induce high levels of single, SSB and DSB in DNA molecule even at very low energy below than 15 eV.

The main paradigm is that LEEs can play a substantial role in the synergistic effect between radiation and chemotherapy [10]. And that's why certain chemotherapeutics have been used alongside radiotherapy, for a long time. For most of the time it has been thought that the synergism of cisplatin and other Pt-based drugs derived from how (because they bind with DNA to form adducts) they interfere with DNA repair processes after irradiation. Recent studies have shown that these adducts also increase damage to DNA during irradiation. Indeed timing the delivery of radiation to arrive when the concentration of Pt-DNA adducts is greatest in the DNA of cancer cells, produces the greatest synergistic effect. This is the basis of a clinical trial currently underway in some clinics for Glioblastoma Multiform (GBM) (brain cancer) patients [11].

2. Why Low Energy Electrons?

Since low energy electrons (beam of electrons of a well-defined low energy, typically in the range of 0 - 200 eV) can be produced by all types of high energy radiation, studies of low energy particle radiation help us to understand the chemistry induced by high energy radiations. The interaction between high-energy radiation (e.g., γ -rays, X-rays, electrons, and ion beams) and matter produces copious numbers ($\approx 5 \times 10^4$ / MeV electrons per MeV of energy deposited) of non-thermal secondary low-energy electrons [12]. The majority of such secondary electrons have energies below 30 eV and their kinetic energies are distributed between 0-100 eV (Figure 1).

At the energy below than 15 eV, LEEs can break a DNA strand via the formation of a Transient Molecular Anion (TMA) (i.e., resonant electron capture) of a DNA subunit (e.g., base, deoxyribose, phosphate and structural water) [13]. In this mechanism, the sub-unit captures the incoming free electron and the resulting TMA dissociates. The TMA can also auto-ionize, leaving a subunit in a dissociative state, a phenomenon which also damages DNA. The mean free path of the majority of the LEEs varies from 0.1 to 10 nm, they can produce clustered damage within DNA [14].

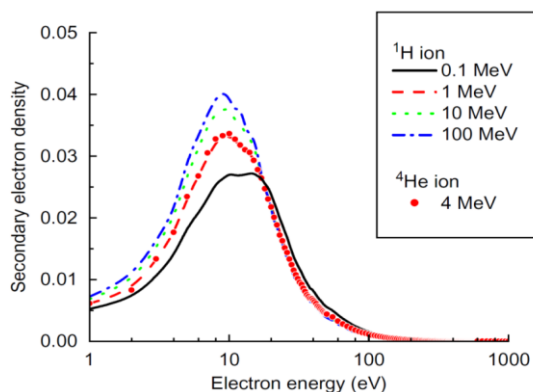


Figure 1. Effect of fast primary protons and $^4\text{He}^+$ ions on the energy distribution of secondary electrons generated in water [10]

Since the mean free path of the majority of the secondary electrons varies from 0.1 to 10 nm, they can produce clustered damage within DNA by depositing their energy within spherical volumes of about the same diameter and dissociates bonds in DNA molecules in a very short time scale (\approx few femtoseconds).

LEEs are capable of chemical selectivity in contrast to high energy ones due to the large number of open dissociative channels in the latter case and their non-resonant nature [4, 15]. In addition to numerous neutral dissociation pathways, LEE can efficiently induce bond ruptures and the formation of highly reactive charged or neutral, atomic or molecular, fragment species via either (a) the various positive (dissociative) ionization channels, in particular near the peak in the ionization cross section (70 – 80 eV), or (b) the many bond specific resonant dissociative electron attachment pathways that open at decreasing LEE energies near or below the ionization threshold and occur down to thermal energies.

In many ways, radiation chemistry is essentially the sum of reactions initiated by secondary LEEs so that much of this chemistry can be studied and understood in the laboratory by investigation of the interactions of energy-selected LEEs with combined chemotropic drugs and plasmid DNA [15].

Understanding radiobiological damage induced by secondary electrons, how this damage can be modified by changing the lifetime of transient anions, the observation of dissociative electron attachment reactions in the 0-20 eV range and the nanoscale dynamics of these

LEEs cannot be studied in real time but only with direct beam experiments is possible.

For instance the Gold Nanoparticles (GNP) are most commonly used for cancer treatment as a novel agents [16], which considerably increase DNA damage induced by high energy radiation by increasing the number of secondary LEEs near DNA and minimize normal tissue toxicity.

Primary beam in conventional radiotherapy, which includes of photons or electrons with energy range of 0.2–20 MeV, would be considered as secondary source of LEEs in the body. LEEs with a wide energy distribution were produced through (Figure 1), their interactions with the cell constituents or biomolecules via different processes such as photoelectric effect and Compton scattering [11].

Some of the chemotherapeutic agents such as cisplatin, carboplatin or doxorubicin, by binding chemically to DNA make the molecule extremely sensitive to secondary LEEs. The formation of TMA by these LEEs leads to local rupture of SSB and DSB in DNA due to a large increase in the magnitude of electron capture. Thus, the abundant LEE produced by high-energy radiation may play a crucial role in increasing radio-sensitivity. The experiments and results, which led to these findings, are studied very well by many researchers [13, 17–19].

Understanding the nanoscale mechanisms of the direct effects of radiation in radio- and chemo-sensitized DNA has implications in the design of new chemotherapeutic and radio-sensitizing drugs, as well as in the development of more efficient protocols in cancer therapy [13]. The addition of DNA-targeted GNP to clinical protocols using platinum drugs could considerably improve concomitant chemo-radiation treatments of cancer.

Given that cancer is the third cause of death in Iran [20], extended research essay about radiation chemistry induced by low energy electrons relevant to the formation of lethal damage to the DNA molecule especially in cancerous cells, helps assign function of cells, identify metabolic and regulatory pathways and suggest targets for diagnostics and therapeutics identify animal models to develop new drugs, among other goals of biomedical interest.

3. Challenges of LEEs in Cancer Treatment

As mentioned before near zero-eV secondary electrons (≤ 0.5 eV) produced by high energy radiations induces lethal damage to DNA [3]. There have been no measurements of the energy distribution or secondary electrons in the cell (in case of dosimetry). Our estimation of those electrons energy is based on experiments on gas and condensed phase measurements with photoelectrons and scattered electrons. Such experiments and basic theory allow the energy distributions to be calculated (via Monte-Carlo simulations) although even then, the calculations are usually for water, rather than the cell (which is largely water). There is some work on secondary electron distribution in DNA, assuming that these simulations are valid, and that most secondary electrons have energies less than ~ 30 eV. Now the main challenge related to using of LEEs in cancer treatment is what happens when you irradiate biomolecules with electrons of similar energy. For example 0.5eV electrons combined with platinum drugs (modified DNA) can induce DSB whereas, normally a ~ 6 eV is necessary to break unmodified DNA [10]. By controlling the electron energy it becomes possible to identify different ways in which electrons can damage DNA. However, there are still many questions with regard to the optimal combinations of LEEs and anticancer agents to maximize the synergistic effects.

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