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A brief review of cancer treatment and DNA damage using Auger effect or low-energy electrons

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A B S T R A C T

Introduction: Despite advances in cancer therapy, many treatments result in significant side effects and inconsistent remission. This review was aimed at exploring the potential of Auger electrons (AEs) as a novel, highly localized approach to cancer treatment.

Materials & Methods: Relevant studies were reviewed to examine the mechanism of action of AEs emitted from radioisotopes, their DNA-damaging effects, and their selective activity in cancer cells. The analysis also included recent developments in cancer cell detection based on surface charges, radionuclide delivery systems, and the role of proton tunneling and low-energy electrons in DNA disruption.

Results: Auger electrons, characterized by low energy and high linear energy transfer (LET), induce lethal DNA damage with minimal impact on surrounding healthy tissue. They act through direct DNA interaction or indirectly via water ionization. Detection methods based on cell surface charge properties showed promise in improving cancer cell targeting. Additionally, advancements in radionuclide carriers enhanced delivery precision. Insights into proton tunneling supported the biological relevance of low-energy electrons in therapeutic applications.

Conclusion: Auger electron therapy offers a promising, targeted strategy for cancer treatment with reduced collateral damage. Continued research is needed to refine delivery systems and better understand electron-cell interactions to maximize therapeutic outcomes.

Keywords: Radioisotopes, DNA Damage, Neoplasms

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Introduction

Electron capture (EC) is a process where an atom's nucleus captures one of its inner orbital electrons, usually from the K-shell, converting a proton into a neutron and emitting a neutrino (1). This process occurs in certain unstable nuclei, known as radionuclides, as they seek stability (2). The neutrino carries away excess energy, and the resulting vacancy in the electron shell is often filled by electrons from higher energy levels, leading to the emission of characteristic X-rays or Auger electrons (3) (Figure 1). Internal Conversion (IC) is another decay process in which an unstable nucleus transfers its excess energy directly to an inner orbital electron, ejecting it from the atom (4).

This ejected electron, called an IC electron, creates a vacancy in the inner shell, which is subsequently filled by electrons from higher orbitals. The energy difference between orbitals results in the emission of Auger electrons or characteristic X-rays (4) (Figure 1).

Auger electrons, first observed by Pierre Auger in 1925, are low-energy electrons emitted following EC or IC processes. These electrons typically have energies ranging from 2 to 50 eV (5). However, Table 1 shows that certain radionuclides emit Auger electrons with significantly higher average energies, such as 193mPt (27.4 keV) and 195mPt (23.1 keV). Auger electrons play a significant role in scientific and medical fields, including cancer treatment and imaging technologies (6).

In cancer treatment, Auger electron emitters (AEs) are used for targeted radiotherapy. Unlike traditional high-energy radiation therapies that utilize photons or beta particles, Auger therapy employs low-energy electrons emitted by radionuclides localized near cancer cells (7). This localized emission minimizes damage to surrounding healthy tissues, making it an attractive treatment option. Radionuclides like 111In (average IC electron energy: 176.1 keV) and 195mPt (average AE energy: 23.1 keV) are particularly effective due to their high energy deposition capabilities (Table 1) (8).

The unique characteristic of Auger electrons is their short range in biological tissues, typically a few nanometers, and their ability to deposit high linear energy transfer (LET) locally (8).

These properties ensure effective damage to cancer cells while sparing adjacent healthy tissues, enhancing the therapeutic index of radiotherapy (9). Many radionuclides used in nuclear medicine imaging, such as Technetium-99m (99mTc), Iodine-123 (123I), Indium-111 (111In), and Gallium-67 (67Ga), undergo EC and IC decay processes (10).

Table 1 provides an overview of radionuclides that emit Auger and IC electrons, summarizing their half-lives, the number of electrons emitted per decay, and corresponding energy levels (10,11). For instance: 99mTc emits an average of 0.9 Auger electrons per decay, with an average energy of 0.2 keV (11). 123I emits 13.7 Auger electrons per decay, with an average energy of 7.2 keV (11). 111In emits IC electrons with an average energy of 176.1 keV (Table 1) (11).

These properties make Auger electron-emitting radionuclides ideal for minimizing collateral damage in surrounding healthy tissues while delivering localized, high-intensity energy to cancerous cells (12). While most Auger electrons have energies below 80 eV, some radionuclides emit electrons with higher energies, contributing to their diverse applications in targeted radiotherapy (13). The energy of Auger electrons, measured in electron volts, can be expressed mathematically as shown in Equation. (1) (14):

$$E_{Auger} = E_K - EL_1 - EL_{2,3} - f$$

, Equation. (1) , (14).

where are the binding energies of the K, L1, and L2,3 electron shells, respectively, and is the work function,

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which is the minimum energy required to release an electron from the surface of a material (14).

Materials and methods

This study is a review article; therefore, no experimental materials or methods were used. Instead, data and findings were gathered from various research sources. The study evaluates Auger electron emissions and their applications by analyzing results from existing literature. Information was extracted from published studies, employing statistical evaluations where applicable. The review incorporated data processed using statistical tools, though no specific program, significance levels, or direct calculations were involved in this wor

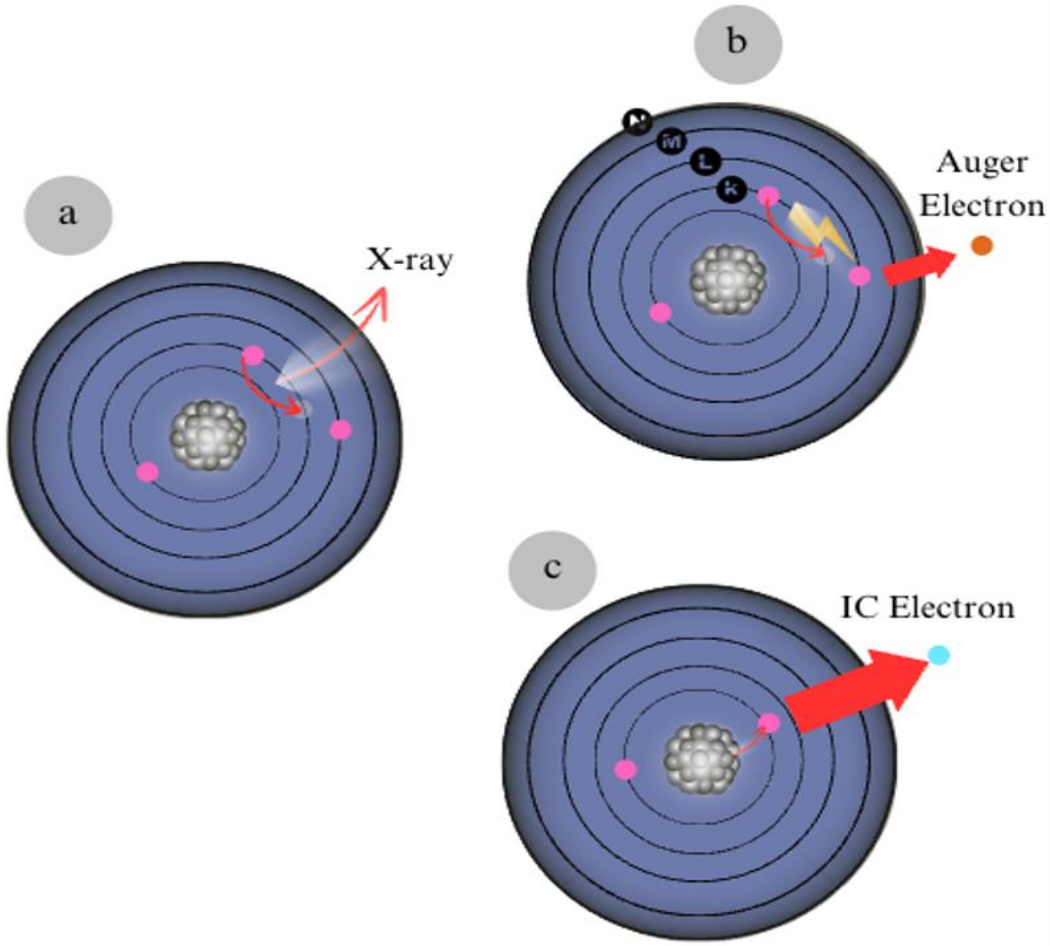


Figure 1. Auger electron emission can occur via electron capture (EC) or internal conversion (IC). In EC, a K-shell electron is captured, creating a vacancy filled by an L-shell electron, leading to either X-ray emission or Auger electron ejection. This process causes progressive vacancies in higher shells. In IC, unstable nuclei transfer energy to eject an electron, also resulting in an inner-shell vacancy.

Table 1. Characteristics of radionuclides that emit Auger electrons. (The quantities of Auger electrons (AEs) and internal conversion (IC) electrons were sourced from the MIRD Radionuclide and Decay Schemes (6,15)).

Radionuclide	Half life	AEs/decay	Average AE energy per decay (keV)	Average energy per AE (keV)	IC electrons \decay	Average IC electrons energy released per decay (keV)	Average energy per IC electron (keV)

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^{125}I	57d	23	12	0.5	0.9	7.3	7.7
^{123}I	13h	13.7	7.2	0.5	0.2	21	222.6
^{67}Ga	78h	5	6.6	1.3	0.3	29.7	14.1
^{99}mTc	6h	4.4	0.9	0.2	1.1	15.2	13.8
^{111}In	67h	7.4	6.9	0.9	0.2	27.9	176.1
^{201}Tl	73h	20.9	14.8	0.7	0.9	29.9	32.9
^{191}Pt	2.8 d	14	17.8	1.3	304	57.1	0.2
^{193}mPt	4.3 d	27.4	10.9	0.4	3	126.8	42.4
^{195}mPt	4.0 d	36.6	23.1	0.6	2.8	161.4	58.1
^{197}Hg	64.1 h	23.2	16.1	0.7	0.8	54.1	67
^{197}mHg	23.8 h	19.4	13.5	0.7	1.6	203.5	127
^{119}Sb	38.2 h	23.7	8.9	0.4	0.8	17	20.2
^{161}Tb[1]	6.9 d	0.9[a]	5.1[b]	5.7	1.4	36.7	26.2

a The quantities of Auger electrons (AEs) and internal conversion (IC) electrons for 161Tb were obtained from the National Nuclear Data Center. (6, 16) b Calculation based solely on Auger electrons from the K and L shells. (6)

Detection of Cancer Cells Based on Their Surface Charges

Although the negative surface charge of cancer cells has been observed, it remains insufficiently understood from a biophysical perspective. Studies indicate that cancer cells exhibit negative surface charges, a feature linked to their secretion of lactic acid due to elevated glycolysis rates, which is a hallmark of cancer metabolism (17). To utilize this property, researchers have developed nanoprobes—electrically charged, fluorescent, and superparamagnetic—that can sensitively detect cancer cells based on their surface charges. These nanoprobes attach to cancer cells through electrostatic interactions, enabling magnetic separation and allowing for differentiation between cancerous and normal cells based on metabolic variations (17).

Tests conducted on 22 cancer cell types from various organs revealed that all cancer cells exhibited negative charges, strongly binding to positively charged nanoprobes (18). Normal cells, in contrast, showed minimal binding, suggesting they are neutral or slightly positive. This differentiation demonstrates the potential of charged nanoprobes for highly selective cancer detection (18). Furthermore, cancer cells can be identified, bound electrostatically, and magnetically separated from blood using charged or superparamagnetic nanoprobes (19). This approach holds promise for removing circulating tumor cells (CTCs) to reduce metastasis risks. If successfully applied in clinical practice, these nanotechnologies could revolutionize cancer detection and treatment options (18, 19).

Cancer Cell DNA and Metabolism

The DNA of cancer cells does not differ in electrical charge from that of normal cells, as DNA is electrically neutral, with a balanced number of negatively charged electrons and positively charged protons. However, cancer cells exhibit distinct metabolic differences compared to normal cells (20). One significant metabolic change in cancer cells is the Warburg effect, a reprogramming that shifts energy production toward glycolysis, even in the presence of oxygen (21). This metabolic adaptation increases glucose consumption and lactate production and favors fermentation over oxidative phosphorylation, the primary energy pathway in normal cells (21, 22).

Although these changes may alter proton concentrations and pH levels within cancer cells, they

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do not impact the electrical charge of DNA (22). While DNA neutrality in cancer cells remains unchanged, these metabolic alterations can indirectly influence the cellular environment (23). Understanding the interplay between cancer cell metabolism and their microenvironment can provide critical insights for developing novel treatment strategies (23).

Slow Electrons in Cancer Treatment and Auger Resonance

Ion beam therapy is a common method for treating cancer, where charged atoms are directed towards tumors to destroy cancer cells. The destruction is primarily caused by slow-moving electrons, which transfer energy to surrounding electrons (24).

A key and complex mechanism known as interatomic Coulombic decay allows ions to transfer more energy to adjacent atoms and release multiple slow electrons, which are ideal for damaging cancer cell DNA (24).

Researchers at the Vienna University of Technology demonstrated that this mechanism is crucial for improving the effectiveness of ion therapy. Their findings showed that when fast ions penetrate materials, they create a cascade of slow electrons, which are more likely to damage DNA than faster electrons. These researchers demonstrated the importance of interatomic Coulombic decay in generating slow electrons using charged xenon ions and graphene. This discovery is vital for refining cancer treatments and protecting space crews from cosmic radiation (24).

Researchers at the University of California developed a nanoscale drug delivery system for treating cancers that have metastasized to the central nervous system, which is particularly challenging due to the blood-brain barrier (25).

This nanocapsule, approximately one nanometer in size, is coated with 2-methacryloyloxyethyl phosphorylcholine (MPC), allowing it to penetrate the barrier and release the cancer drug rituximab. In mice, the nanocapsule effectively reaches metastasized cancer in the central nervous system. This method eradicates B-cell lymphoma that has metastasized to the central nervous system. This innovative approach has the potential to treat various cancers and brain diseases (25).

In 1997, it was predicted that an electronically excited atom or molecule in a system with a weak bond, such as a cluster with hydrogen or van der Waals bonds, could transfer its excess energy to neighboring species, resulting in the emission of a low-energy electron (26).

This process, known as intermolecular Coulombic decay (ICD), has been repeatedly observed and raises questions about its role in DNA damage caused by ionizing radiation, where low-energy electrons are significant (27).

Recent suggestions have indicated that ICD can be effectively induced by resonant excitation of the nucleus of a target atom, which then undergoes Auger decay, creating an ionized species with sufficient energy for ICD (28).

This study experimentally demonstrated that Auger resonance decay can induce ICD in nitrogen and carbon monoxide dimers. Using ion and electron momentum spectroscopy, the experiment showed that ICD occurs in less than 20 femtoseconds, faster than the dissociation of individual molecules. This experimental confirmation may inspire new methods for localized cancer radiotherapy using resonant X-ray stimulation. The process involves initial resonant excitation of a K-shell electron, followed by Auger decay to an ionized state that can undergo ICD (28).

This mechanism was thoroughly investigated using carbon monoxide and nitrogen dimers and showed that resonant Auger decay leads to a continuous range of kinetic energy values, consistent with ICD. The measured kinetic energy release for nitrogen and carbon monoxide dimers matched theoretical estimates and supported the presence of ICD (28).

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The sequence of events depicted in FIGURE 2 illustrates the resonance-based Intermolecular Coulombic Decay (ICD) mechanism. Panel (a) shows the excitation of a molecule within a molecular dimer through a resonant process. This excitation involves the absorption of energy by the molecule's nucleus, indicated by the upward arrow (29).

In panel (b), this excited state of the nucleus decays via a spectator Auger process, which leads to the formation of a highly excited molecular ion state. The energy transfer from the excited molecule to its neighbor is depicted in this phase. Finally, in panel (c), the ICD process takes place, where the excitation energy is transferred to the neighboring molecule, resulting in the emission of a low-energy ICD electron, as shown by the red arrow (29).

This electron emission is significant for the context of cancer treatment, as it plays a role in damaging DNA. This process is crucial for understanding how localized radiotherapy can be enhanced using resonant X-ray stimulation, as outlined in the study by Li et al. (29).

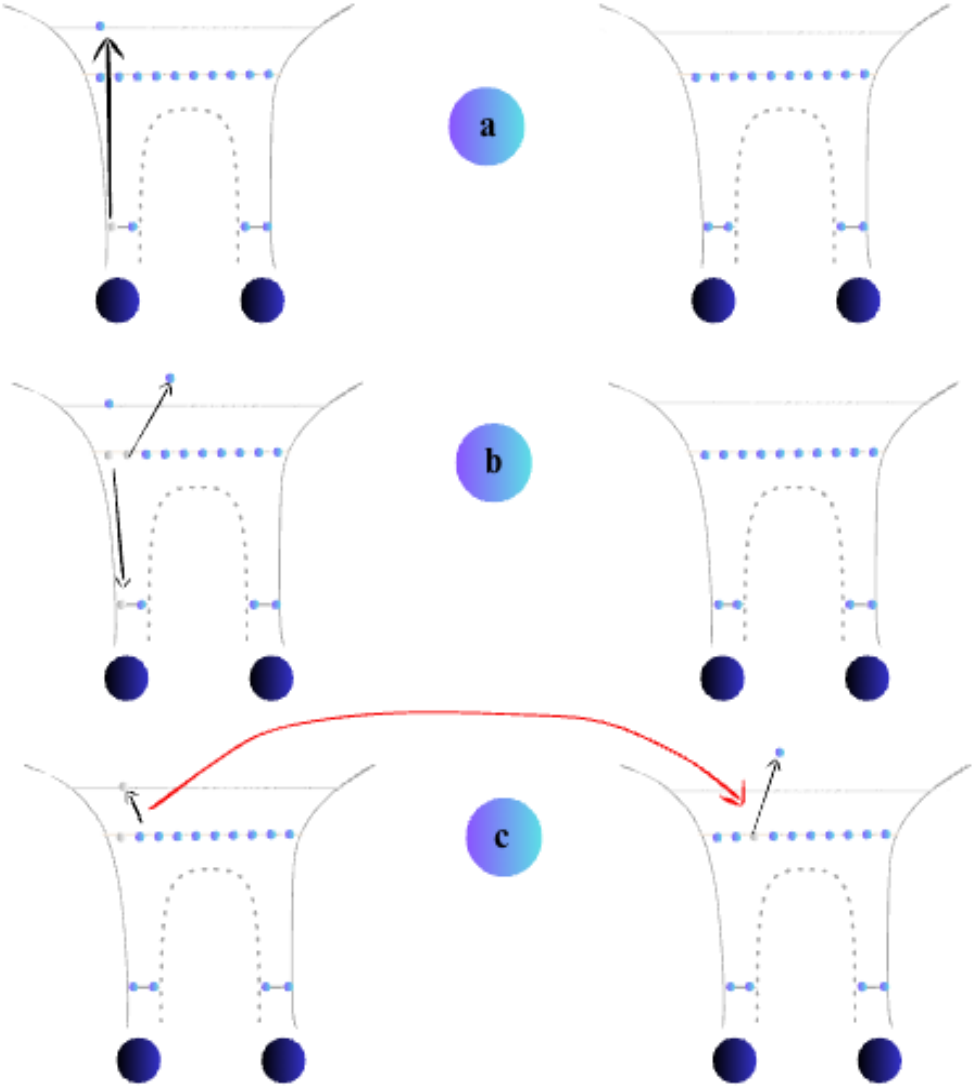


Figure 2. The decay cascade mechanism involves the following steps: a) A molecule in the molecular dimer is core-excited. b) The core-excited state decays through spectator Auger decay, leading to a highly excited molecular ion. c) Interatomic Coulombic Decay (ICD) transfers the excitation energy to a neighboring molecule, which then emits a low-energy ICD electron (28).

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Attosecond Electron Bunches and Observing Auger Electron Effects in DNA

An attosecond (10^{-18} seconds) is a remarkably brief unit of time, essential for studying the rapid changes that occur within the realm of electrons (30). The 2023 Nobel Prize winners in Physics have created light pulses so short that they are measured in attoseconds, enabling the imaging of processes within atoms and molecules (31). Attosecond pulses offer valuable insights into internal material processes and the identification of various events. These pulses have been instrumental in revealing details of atomic and molecular physics, with potential applications in fields such as electronics and medicine (32).

For example, attosecond pulses can be used to examine molecules, which emit distinct measurable signals. These signals act as fingerprints, indicating specific molecular structures and potentially assisting in medical diagnostics (32). This technique can be employed to study the behavior of Auger electrons, slow electrons, and low-energy electrons, and their effects on cancer cell DNA. Attosecond pulses allow for measuring the time it takes for an electron to detach from an atom, providing insights into which electron reactions are most effective at damaging cancer cell DNA.

How do physicists use these ultrashort pulses to create attosecond-scale films of electrons? Traditional films are made by capturing each moment as a frame with a camera and stitching them together to form a complete sequence (33). Attosecond electron films utilize a similar concept. Attosecond pulses act like flashes, illuminating electrons so that researchers can capture their motion repeatedly—similar to filming a scene. This technique, known as pump-probe spectroscopy, involves a "pump" pulse that initiates electron movement, starting the "film." A "probe" pulse then illuminates the electron at various intervals after the pump pulse, allowing it to be captured by a "camera," such as a photoelectron spectrometer (33). Although directly imaging electron movement within atoms is challenging, researchers have developed various advanced microscope techniques to achieve this. In pump-probe spectroscopy, the photoelectron spectrometer can detect the number of electrons ejected from an atom by the probe pulse, while a photon spectrometer measures the amount of probe pulse absorbed by the atom (34). These different "scenes" are then combined to create attosecond films of electrons. These films provide valuable insights into attosecond electronic behavior, enhanced by theoretical models (34).

For instance, some researchers have calculated the position of electric charge in organic molecules at different times on an attosecond scale, enabling control of electric currents at a molecular level (35). By analyzing these films with appropriate systems or devices, significant progress can be made in cancer treatment using Auger electrons, slow electrons, and low-energy electrons. Such a device could function similarly to a PET scan (positron emission tomography), providing detailed information about electron behavior (36). This data, if accurately interpreted, can explain what occurs after Auger electrons impact cancer cell DNA, potentially leading to improved cancer treatments. Moreover, software compatible with attosecond devices can be used for data analysis (36).

Auger Electrons, Proton Tunneling in DNA, and Cancer Cells

Low-energy electrons (LEE) and Auger electrons both play significant roles in surface science and material analysis, although there are differences in their origins and production processes. Low-energy electrons result from the inelastic scattering of primary radiation, while Auger electrons are produced through an internal atomic relaxation process (37).

Despite these differences, their surface sensitivity and influence on material properties provide common ground for their applications and detection methods (37). In FIGURE 3, the Watson-Crick model depicts

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DNA as a double helical structure composed of sugar-phosphate chains held together by nucleotide base pairs connected by hydrogen bonds. In this model, adenine (A) pairs with thymine (T), and guanine (G) pairs with cytosine (C), forming complementary base pairs essential for DNA replication and the transmission of genetic information (38). The model also suggests that mutations can occur when one of the bases undergoes a rare tautomeric shift, leading to errors in the genetic code. Experimental evidence indicates that chemical compounds, such as nitrous acid, can induce mutations by altering the proton-electron pairing in DNA bases (38). Researchers have employed density functional theory (DFT) and molecular dynamics to simulate DNA damage caused by low-energy electron attachment. These simulations focused on anionic single nucleotides of DNA in an aqueous environment, analyzing the influence of surrounding water molecules on radiation damage mechanisms (39).

The findings revealed that hydrogen bonding and the protonation of nucleotides by water significantly alter the energy barriers for DNA strand break reactions (39, 40).

Furthermore, ionizing radiation can damage DNA in living cells, potentially causing mutations and diseases, including cancer (40).

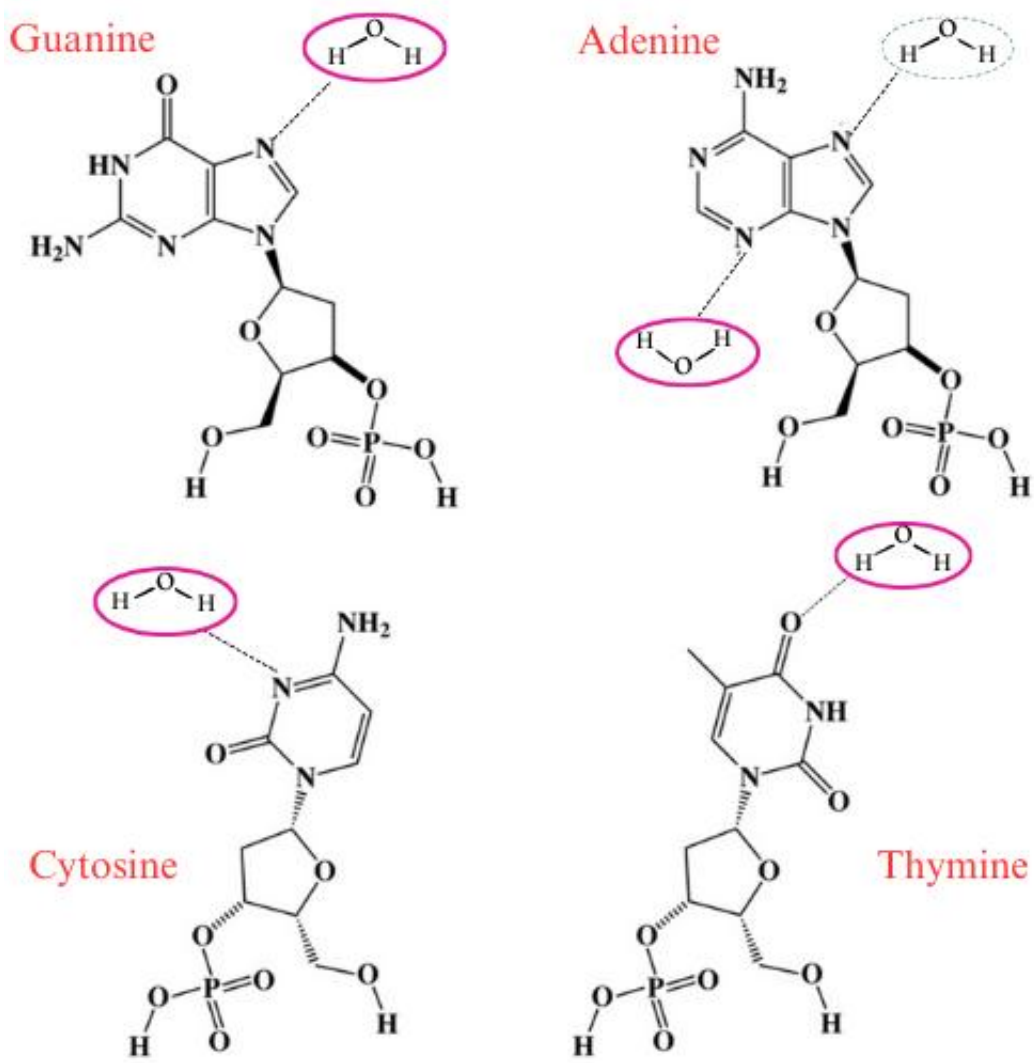


Figure 3. Hydrogen Bonding in DNA Nucleotides and Water Interactions. This figure illustrates the chemical structure of DNA nucleotides (Guanine, Adenine, Cytosine, and Thymine) and their interaction with water molecules through hydrogen bonding.

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The pink-circled regions highlight water molecules forming hydrogen bonds with nucleotides, emphasizing the role of water in stabilizing the DNA structure and influencing biological processes such as replication and repair (41).

In cancer cells, DNA is composed of nucleotides arranged in a double helix structure. Each nucleotide consists of a phosphate group, a sugar molecule (deoxyribose), and one of four nitrogenous bases: adenine (A), thymine (T), cytosine (C), or guanine (G) (42).

The sequence of these bases encodes genetic information that determines the characteristics and functions of cancer cells. A defining feature of cancer cells is the accumulation of mutations or genetic alterations, which can lead to uncontrolled cell growth and the invasion of neighboring tissues (41). These mutations may result from environmental factors, genetic predispositions, or errors during DNA replication and repair processes (42, 43). Additionally, cancer cells often exhibit changes in other components of their genetic material, including epigenetic modifications (chemical tags that regulate gene expression) and structural or organizational alterations in chromatin, the DNA-protein complex in the nucleus (43). Understanding DNA damage mechanisms at the molecular level is crucial for improving cancer treatments such as radiotherapy (44). While ionizing radiation can directly damage DNA, low-energy electrons generated by the radiolytic breakdown of water are particularly harmful, causing more strand breaks than oxidative damage by OH radicals (45).

Water plays a pivotal role in this process, as it alters the potential experienced by excess electrons and influences the dynamics of the resulting fragments (46). Simulations suggest that water molecules can either shield DNA from damage or enhance its susceptibility to strand breaks (47).

The mechanism by which low-energy electrons cause DNA strand breaks involves electron attachment, forming transient negative ions. Depending on energy barriers and anion resonance states, this process may lead to dissociative electron attachment (DEA) (47).

In one study, researchers employed density functional theory and molecular dynamics simulations to investigate DNA nucleotides in water, focusing on protonation reactions and strand breakage (48). The findings revealed that protonation significantly influences DNA reactivity, as most anions are likely to become protonated, thereby modifying the barrier to strand breakage. This highlights the critical role of the aqueous environment in modulating DNA damage, where protonation of DNA anions can potentially prevent strand breaks (48). Hydrogen bonds are crucial for the complementarity between nucleotide bases. The properties of these bonds, including their strength and formation, have been extensively studied (49). Proton sharing between single-electron pairs is fundamental to hydrogen bond formation, while the electronic structure of atoms involved in these bonds highlights the role of proton absorption (49). The phenomenon of proton hopping, governed by activation energy and quantum mechanics, and the concept of proton tunneling, where a proton penetrates forbidden regions, are significant in understanding hydrogen bonding (49). Proton tunneling in DNA plays an essential role in maintaining the stability of hydrogen bonds within DNA base pairs, ensuring accurate transmission of genetic information.

However, proton tunneling can also lead to base transfer and mutations, which may affect the genetic code (50). These mutations are linked to aging, spontaneous tumor formation, and cancer development, as they influence abnormal cell growth and malignant tumor formation. External factors, such as radiation and magnetic fields, also impact proton tunneling in DNA, altering its biological implications. This discussion underscores the complex relationship between proton tunneling and its influence on genetic stability and disease (50).

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Conclusion

Auger electron therapy has been extensively studied as a highly localized approach for cancer treatment. Findings from multiple studies demonstrated that Auger electrons exhibit high linear energy transfer (LET) within a short range, making them effective in inducing targeted DNA damage while minimizing harm to healthy tissues (51).

Comparative analyses with conventional radiation therapies revealed that Auger electron therapy significantly reduces off-target effects and enhances therapeutic efficacy in localized tumors (51).

The review also highlighted that radionuclides such as 111In, 123I, and 195mPt have shown promising results in clinical and preclinical studies, effectively delivering Auger electrons to tumor sites. Additionally, recent developments in nanoparticle-based delivery systems and molecular targeting strategies have further improved treatment precision (52).

These advances suggest that Auger electron therapy could be a powerful tool in oncology, particularly for tumors located in sensitive regions where minimizing damage to surrounding tissues is crucial (52).

However, despite these promising results, challenges remain in fully understanding the underlying mechanisms of Auger electron-induced DNA damage, particularly regarding proton tunneling and secondary molecular interactions. Further studies are required to clarify these pathways and optimize radionuclide delivery (52).

Future developments should also focus on improving imaging techniques, integrating Auger therapy with positron emission tomography (PET), and exploring attosecond pulse technology to study electron interactions at the atomic level. These advancements could lead to more personalized and efficient cancer treatment strategies, ultimately expanding the clinical applications of Auger electron therapy.

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Authors' contributions

Conceptualization, Methodology, Validation, Formal Analysis, Data Curation, Writing– Original Draft Preparation, Supervision, Project Administration: ME, Investigation, Resources, Writing– Review & Editing, Visualization: SA.

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