Chapter 4

The Role of Radiation on Ion Channels: Molecular Mechanisms, Cellular Responses, and Clinical Implications

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Abstract

Radiation is defined as the transmission of energy in the form of electromagnetic waves or rapidly moving particles. Essentially, radiation is defined as the process of energy emission and transport in a medium. With the increasing use of radiation in various fields, the harmful effects of ionizing and non-ionizing radiation on human health have become apparent over time. In particular, for ionizing radiation to cause biological damage in a living organism, the radiation energy must be absorbed by the cell. This absorption results in ionization and excitation in the target molecules. These ionizations, which are the initiating events for subsequent biological damage, can cause breaks in the DNA strands carrying the cell's genetic information and the production of chemical toxins within the cell. Today, radiation plays a vital role in diagnostic imaging and cancer treatment in medical applications. This vital process is meticulously regulated by transmembrane proteins called ion channels, which allow the selective passage of ions across the cell membrane. These proteins play a role in most physiological processes, including the electrical excitability of heart and neuronal cells, cell growth and proliferation, and hormone secretion. Deficiencies in the normal functioning of these channels are considered disorders that negatively affect life. Among ion channels, transient receptor potential (TRP) channels stand out in particular. The 2021 Nobel Prize in Medicine was awarded to scientists who elucidated the molecular basis for sensing heat, cold, pain, and mechanical force. This was for their work on the TRPV1 channel within the TRP ion channel family in the cell membrane. Future research on ion channels will pave the way for understanding the biological effects of radiation and discovering new drugs to counter these effects.

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1. Indroduction

In its most basic sense, radiation can be defined as energy traveling through or scattered in a medium. It is divided into two groups: ionizing and non-ionizing. Ionizing radiation, in particular, is high energy that causes damage to biomolecules by creating free radicals through energy transfer in living tissues. It can cause breaks in the DNA chain directly or indirectly. These oxygen radicals interact with DNA components, leading to damage. Although cell types have different sensitivities to radiation, it is known that cells that divide frequently and are undifferentiated have a higher sensitivity, while cells that do not divide and show higher differentiation have a lower sensitivity (Figure 1) [1].

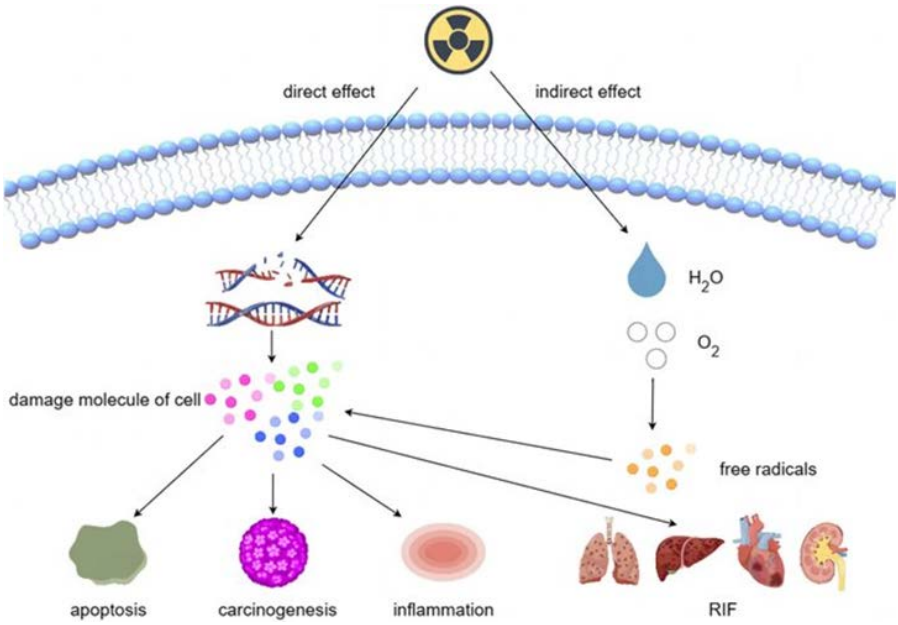

Figure 1. Biological effects of radiation [2].

2. Types of Radiation and Mechanisms of Cellular Damage

2.1. Ionizing Radiation

The physicochemical changes caused by ionization and excitation events in living matter caused by high-energy ionizing radiation, which can detach electrons from atoms, occur in less than a second. However, it takes time for the biological consequences of these physicochemical changes to appear [3]. Ionizing radiation travels like microscopic projectiles, giving energy to

the matter it encounters until it is stopped and absorbed. It also breaks the molecular bonds of the matter along its path, causing changes in the structure of the matter. Living cells mostly consist of long protein chains, and when a cell is exposed to radiation, some of the bonds between these molecules break. The resulting small molecular fragments randomly bind together, forming new molecules. These newly formed molecules are unable to perform their normal functions and need to be repaired. Otherwise, damaged molecular structures will accumulate in the cell, the cell's metabolism will change, and damaged DNA molecules will lead to cancer formation. Cells have certain repair mechanisms to remedy such damage. In fact, cells in advanced organisms prefer to break down and rebuild all molecules at certain intervals, whether damaged or not, rather than individually checking and repairing damaged molecules. However, the cell's repair capacity is limited, and when this limit is exceeded, damaged molecules begin to accumulate, and the cell's life functions are affected. No cell is completely resistant to radiation. The nucleus, and especially the chromosomes in the process of division, are much more sensitive to radiation than the cytoplasm of the cell. One of the most prominent effects of radiation at the cellular level is the suppression of cell growth. In particular, growth is interrupted in cells exposed to radiation during mitosis. Ionizing radiation can cause chromosomes to break, stick together, interlock, and curl. Chromosome breaks can reorganize, remain the same, or fuse with another chromosome. All these events can result in mutation or, further, lead to the death of the cell [4].

The adverse effects of ionizing radiation on a biological system are divided into two categories: direct and indirect effects. If radiation energy is absorbed by DNA or an enzyme molecule, the adverse effects it creates on these molecules are called the direct effects of radiation. If enough energy is absorbed to remove an electron from the molecule, bond breaks occur. Two types of bond breaks can occur: single or double bond breaks. Single bond breaks can usually be repaired by the cell, but double bond breaks usually cause cell death. If the radiation energy is not directly absorbed by the molecules in the biological system, but is absorbed by the molecules of the environment in which the system is located and affects it indirectly by causing a change in the environment, this is called the indirect effect of radiation. In the indirect effect, free radicals are formed as a result of energy transfer due to radiation. As a result of these free radicals affecting DNA, some damage occurs [5].

2.2. Non-Ionizing Radiation

Non-ionizing radiation encompasses electromagnetic fields that lack sufficient energy to dislodge tightly bound electrons from atoms, including

radiofrequency waves, microwaves, infrared, and visible light. Unlike ionizing radiation, which directly causes DNA breaks, non-ionizing radiation primarily interacts with biological tissues through mechanisms such as thermal effects, changes in membrane properties, and modulation of cellular signaling pathways [6]. Experimental studies have shown that prolonged exposure to certain types of non-ionizing radiation can affect ion channel activity, oxidative stress levels, and gene expression, although the biological significance of these changes is still being investigated. Clinically, non-ionizing radiation is widely used in diagnostic imaging (e.g., MR), therapeutic modalities (e.g., laser therapies), and communication technologies, highlighting its dual role as both a valuable biomedical tool and a potential environmental health concern [7, 8, 9].

3. Ion Channels: Classification, Structural Characteristics, and Radiation Susceptibility

Ion channels constitute a large family of integral membrane proteins expressed in almost every cell type, particularly in excitable and non-excitable cells. They utilize transmembrane potential and ionic concentration differences to regulate the passive and rapid passage of ions across the cell membrane. Ion channels also control electrical and biochemical signals, thus playing a role in regulating numerous different physiological processes, including the modulation of neuronal excitability, muscle contraction, neurotransmitter and hormone release, cell proliferation, and cell volume. An ion channel is defined as an integral membrane protein that provides at least a regulated ion-permeable pathway across the cell membrane. Once opened, ion channels exhibit selectivity toward the class of ions allowed to pass through. Some ion channels allow only a specific cation or anion to pass through; for example, sodium (Na^+) channels allow only Na^+ ions to pass through, while potassium (K^+) channels allow only K^+ to pass through [10].

Ion channels are divided into two different groups: gated and ungated ion channels. Ungated ion channels are continuously open to ion passage. Gated ion channels are transmembrane ion channels that open and close in response to the binding of a chemical messenger. They are classified according to their responses to environmental factors. Ion channels open in response to changes in membrane potential. Based on the way they open, ion channels are basically divided into four types: voltage-sensitive ion channels, ligand-gated ion channels which open upon binding of a ligand such as a hormone or neurotransmitter, mechanically sensitive ion channels, and leakage channels [11].

3.1. Voltage-Sensitive Ion Channels

Voltage-sensitive ion channels play a central role in regulating the functions of electrically excitable cells (Figure 2). They control the passage of ions by responding to changes in membrane potential and are critical in fundamental biological processes such as nerve transmission, muscle contraction, regulation of heart rhythm, and hormone secretion. Therefore, they are of great importance both for the continuation of normal physiological processes and in the treatment of various diseases. Voltage-sensitive ion channels, Na^+, K^+, and calcium (Ca^{2+}) channels, open and close in response to changes in membrane potential. The main effect of radiation on these channels is based on the oxidative modification of channel proteins and the alteration of gating kinetics [12].

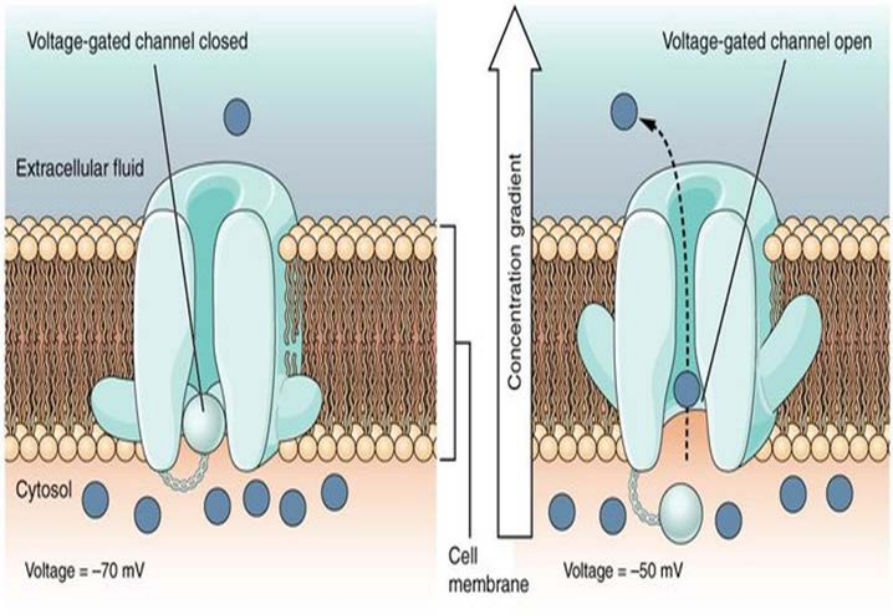

Figure 2. Voltage-Sensitive Ion Channels [13].

3.2. Ligand-Gated Ion Channels

In ligand-gated ion channels, the opening and closing of the channel gate occurs when a specific ligand, such as chemical agents or neurotransmitters, binds to the channel [14]. Ligand-gated ion channels have ligand-binding sites on the inner surface of the cell, which operate via secondary messengers (Figure 3). These channels can be permeable to all physiological cations or to specific ions such as K^+, Cl^-. The conversion of intracellular chemical

signals into electrical information is the primary function of ligand-gated ion channels [15].

Ligand-gated channels such as glutamate (NMDA, AMPA) and GABA receptors play a critical role in synaptic plasticity and neurotransmission. Radiation may contribute to Ca^{2+} overload by indirectly increasing NMDA receptor activity [16].

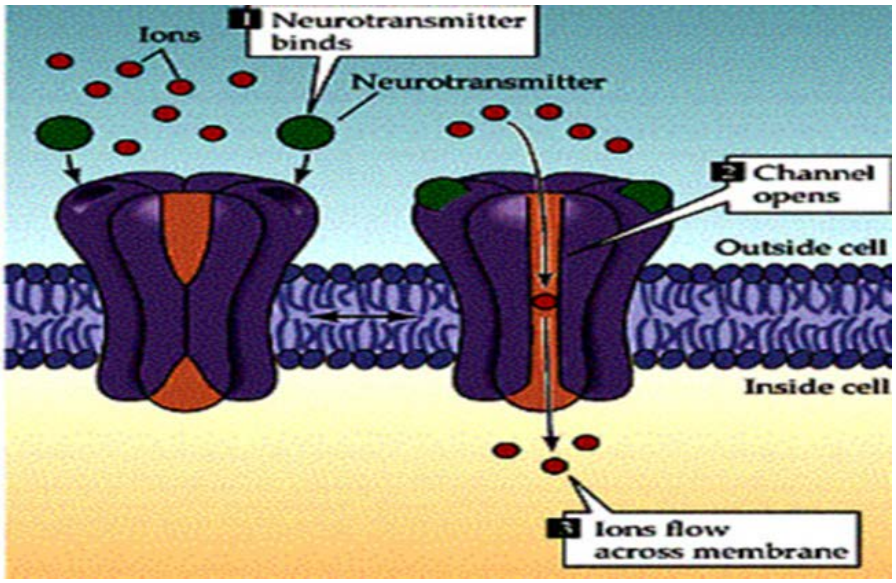

Figure 3. Schematic view of ligand-gated ion channels [17].

3.3. Mechanically Sensitive Ion Channels

The ability to perceive physical forces is preserved in organisms. Channels activated by mechanical stimuli are called mechanically gated ion channels (Figure 4). Cells can convert mechanical stimuli into electrical and chemical signals thanks to mechanically activated ion channels. These channels show activity depending on voltage and pressure. Unlike the senses of touch, hearing and balance, they act as sensors in many systems such as cardiovascular regulation and osmotic homeostasis [18].

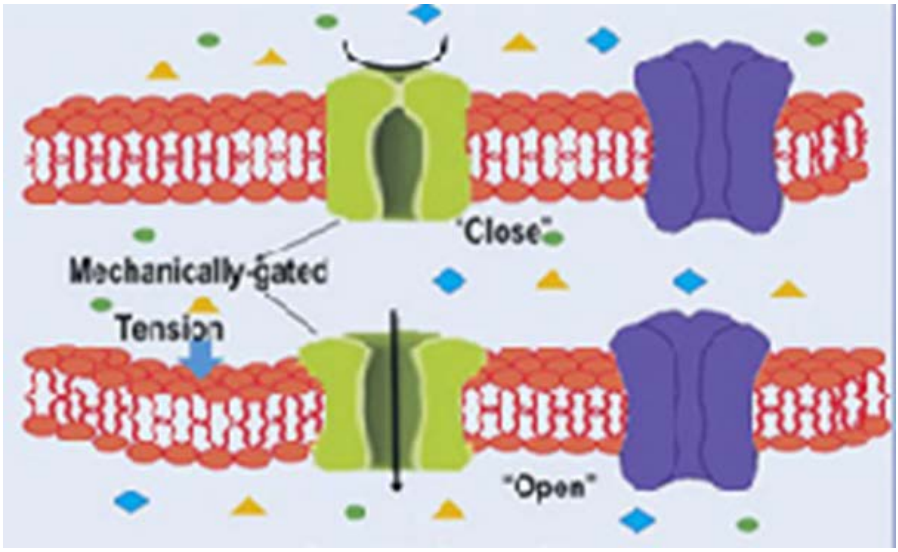

Figure 4. Mechanically sensitive ion channels [19].

3.4. Leakage Ion Channels

The simplest form of ion channels is leakage channels. Some K^+ channels are characterized by the presence of two pore domains. These channels are called 2-Plan K^+ channels. 2P-domain K^+ channels are open at resting membrane potential, therefore they are called leakage channels or background K^+ channels. Leakage channels become voltage-dependent when they are in good contact. Also, some of these channels are closed by the ligand even though they are not ligand-bound [20]. Different leakage channels exist for Na^+, K^+, and Cl^-. K^+ ions leak more than Na^+ ions, and K^+ leakage channels are more numerous. This makes the plasma membrane more resistant to potassium than to other ions [21].

4. Transient Receptor Potential Channels

The Transient Receptor Potential (TRP) protein was discovered in 1969 in a mutant strain of Drosophila melanogaster (fruit fly) that developed visual impairment due to prolonged exposure to light [22]. In the electroretinograms of fruit flies with normal TRP protein, the responses received from the cells to continuous illumination were also continuous. It was determined that as a result of a spontaneous mutation in the gene encoding the TRP protein, a 'transient', or temporary, voltage response was received instead of a continuous voltage response to continuous illumination, and as a result, a visual defect occurred.

The TRP channel superfamily are cation channels known to be permeable to Ca^{2+}, Na^{+}, and K^{+} ions in mammals. TRP channels generally consist of three different regions: the N-terminal region, the transmembrane region, and the C-terminal region. These channels, which have a transmembrane region that crosses the membrane six times, have a pore formed between the fifth and sixth transmembrane regions, allowing Ca^{2+} passage. The amino (N) and carboxyl (C) ends are located inside the cell and become functional by forming homo- or heterotetramers (Figure 5) [23].

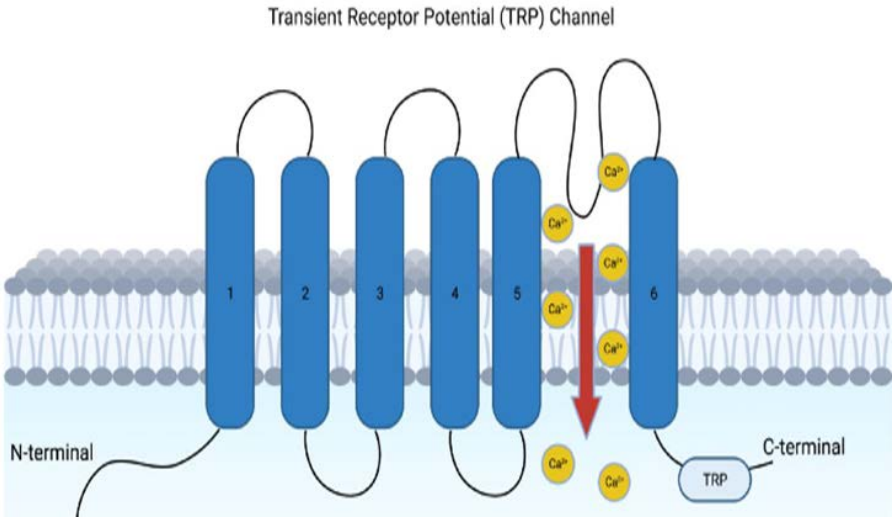

Figure 5. TRP channel structure [24].

TRP channels are activated by chemical, thermal, or mechanical stimuli. They play a role in functions such as oxidative stress, inflammation, pain, and temperature regulation [25, 26, 27]. Pathological expression of TRP channel proteins has been shown to be associated with cancer formation, cancer progression, and apoptosis disorders [28].

TRP channel proteins, which have 28 members in mammals, are non-selective cation channels and are divided into two groups and seven subclasses. TRP channel proteins were discovered by increasing Ca^{2+} concentration in an anaerobic process. They have been studied in various organisms, from yeasts to many mammals. TRP channel proteins, called a superfamily, are divided into 5 main subfamilies: TRPC (canonical), TRPA (ancrine), TRPV (valinoid), TRPN (NOMPC), and TRPM (melastatin). The second family group is further divided into TRPP (polycysteine) and TRPML (mucolipin) (Figure 6). All TRP channels, which have six segments for transmembrane

passage, are capable of transporting Ca^{2+} and show capacity differences among their types [29].

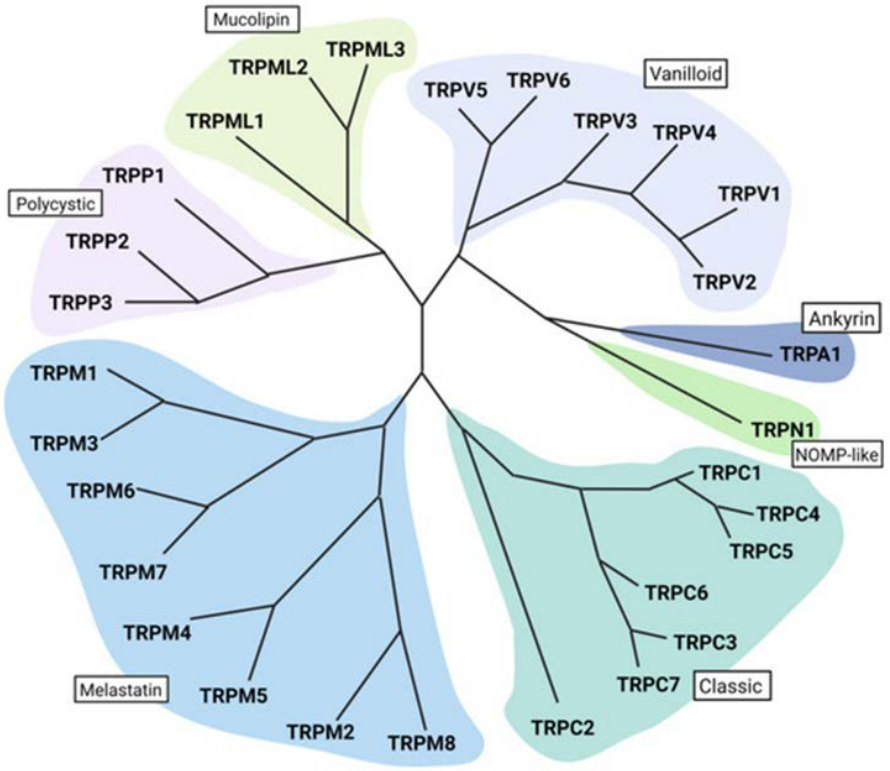

Figure 6. Schematic representation of the TRP channel family [30].

5. The Importance of Ion Channels in Cellular Functions

All living cells are surrounded by a plasma membrane, which separates the inner and outer surfaces of the cell. This plasma membrane in the cell consists of amphipathic phospholipids, which allow uncharged molecules such as CO_2 and O_2 to pass through easily, and proteins, which allow other large molecules such as ions, amino acids, and carbohydrates to pass through. Ion channels, one of these protein complexes, are macromolecular protein complexes that facilitate the movement of ions by being located within the cell membrane (integral) and crossing the membrane [transmembrane]. Ion channels play a fundamental role in the formation and maintenance of membrane potential by enabling selective ion passage across the cell membrane. Ion movement across the membrane occurs through 3-5 Å diameter holes created by ion channels in the membrane. The ion current generated in the

channel constitutes the potential source of the membrane. This is an event that must occur for electrical excitation. These ions passing through the channel can participate in intracellular signaling as the source of secondary messengers. Ion channels mediate the movement of ions such as K^+, Na^+, Ca^{2+}, H^+, and Cl^-. Specific channels for ions are observed in the cell membrane, which is due to the selectivity of the membrane. The functions of these channels are involved in many biological events such as action potential generation, synaptic transmission, muscle contraction, hormone release, and cellular Ca^{2+} balance. Therefore, disorders in ion channel function can lead to a wide range of pathophysiological consequences [31].

6. The Importance of Radiation-Ion Channel Interactions

Radiation disrupts ion homeostasis by directly or indirectly affecting ion channels, triggering cellular stress responses and toxicity. This, in turn, alters electrical activity by affecting the intracellular Ca^{2+}, Na^+, and K^+ balance [32]. Radiotherapy used in cancer treatment allows for new treatment strategies by taking these channels into account. It will have an important role in the discovery of new drugs, especially against the side effects of radiotherapy.

7. Radiation-Sensitive Sensitive Ion Channel Types

Among the various classes of ion channels, voltage-gated Ca^{2+} channels are considered particularly sensitive to ionizing radiation. Their structural and functional disruption leads to profound changes in intracellular calcium homeostasis, triggering oxidative stress, apoptosis, and disruption of cellular signal transduction. Voltage-gated Na^+ and K^+ channels also exhibit radiation-induced gating kinetics alterations that can compromise neuronal excitability and cardiac rhythm stability [33]. The selective sensitivity of these channels highlights their dual roles as potential therapeutic targets in radiotherapy and critical determinants of radiation-induced toxicity in excitable tissues such as the nervous and cardiovascular systems [34].

The interaction between radiation and TRP channels is attracting increasing attention as a key mechanism in cellular stress responses [35]. Functioning as non-selective cation channels sensitive to oxidative stress and membrane disruptions, TRP channels can be modulated directly by ionizing radiation or indirectly through the production of reactive oxygen species (ROS). Radiation-induced activation of TRPM2, TRPV1, and related subtypes leads to abnormal calcium influx, disruption of ionic homeostasis, and initiation of apoptotic and inflammatory pathways [36]. In excitable tissues such as neurons and cardiomyocytes, these changes have contributed to impaired electrical activity and increased susceptibility to radiation-induced toxicity [37]. Consequently,

TRP channels are considered not only as mediators of radiation damage but also as potential therapeutic targets to enhance radiosensitivity in cancer cells while mitigating adverse effects in normal tissues.

8. Effects of Radiation on Ion Channels: Molecular and Cellular Levels

8.1. Radiation-Induced Calcium Dysregulation

Radiation-induced calcium dysregulation represents a crucial mechanism between cellular damage and tissue toxicity. In particular, ionizing radiation can directly alter the structure of voltage-gated calcium channels and the passage properties of ions, or indirectly affect them through oxidative stress and lipid peroxidation, leading to increased calcium influx into the cell. This effect results in disruption of intracellular calcium balance, initiating a series of harmful processes such as mitochondrial dysfunction, activation of apoptotic pathways, and impaired neurotransmitter release [38].

8.2. Changes in Na^+ and K^+ Channels

Ionizing radiation has been shown to cause significant changes in the function and expression of voltage-gated Na^+ and K^+ channels, which are key regulators of neuronal excitability and heart rhythm [39]. Experimental studies show that radiation exposure can alter channel gating kinetics, reduce current amplitudes, and change channel density in the plasma membrane [40]. Mechanistically, these effects are mediated both by direct structural damage to channel proteins and by indirect pathways involving oxidative stress, lipid peroxidation, and DNA damage signaling [41]. Overall, Na^+ and K^+ channels appear to be critical targets of radiation and have an important role in clinical radiotherapy in terms of both neurotoxicity and cardiotoxicity.

8.3. DNA Damage Response and Channel Expression

The interaction between DNA damage response pathways and ion channel expression has emerged as a critical aspect of cellular stress regulation. Ionizing radiation and genotoxic agents not only activate canonical DNA damage response signaling cascades such as ATM/ATR and p53, but also modulate the transcriptional and post-translational regulation of ion channels [42]. Changes in the expression of voltage-gated calcium and potassium channels have been observed following DNA damage, leading to alterations in intracellular ionic balance, mitochondrial function, and apoptotic signaling [43]. These alterations can enhance cellular stress responses, affect radiosensitivity, and influence tissue-specific outcomes, particularly in excitable cells such as neurons

and cardiomyocytes. Therefore, the interaction between DNA damage response mechanisms and ion channel regulation presents a promising area of research for understanding radiation-induced toxicity and developing novel therapeutic strategies in cancer radiotherapy.

8.4. Activation of TRP Channels

Recent scientific studies have highlighted the role of TRP channels in radiation-induced cellular responses. Experimental evidence shows that ionizing radiation can activate TRPM2 and TRPV1 channels via the production of ROS, which can lead to excessive calcium influx and oxidative stress-mediated apoptosis [44]. Patch-clamp recordings and molecular analyses confirm that TRP channel activity is altered after radiation exposure and contributes to mitochondrial dysfunction and inflammatory signaling cascades [45]. In a pain model in mice created after exposure to x-rays, ionizing radiation, Jin Su Cun et al. showed that X-rays activated TRPA1 ion channels [46]. In neural and cardiac models, radiation-induced TRP channel modulation has been associated with impaired excitability and increased susceptibility to tissue damage [47]. In another study, they showed that TRPM2 and Ca^{2+} channels were expressed in the dorsal root ganglion cells of rats exposed to 2.45 GHz electromagnetic radiation using patch-clamp analysis [35]. Overall, these findings suggest that TRP channels serve as both mediators of radiation toxicity and potential therapeutic targets to mitigate adverse effects in radiotherapy.

9. Conclusion

In our rapidly advancing technological age, living completely free from radiation has become almost impossible. We are exposed to both natural and artificial radiation, and we need to elucidate its biological mechanisms of action. In this study, we attempted to investigate the relationship between radiation and ion channels. Our research shows that the interaction between radiation and ion channels plays a significant role in understanding cellular stress responses and tissue toxicity. Ionizing and non-ionizing radiation can directly alter the structural integrity and permeability of ion-gated channels or indirectly regulate their activity through oxidative stress and lipid peroxidation. These disruptions impair ionic homeostasis, particularly calcium, sodium, and potassium influxes, thereby disrupting neuronal excitability, heart rhythm, and intracellular signaling pathways. The dual role of ion channels—as mediators of radiation-induced damage and potential therapeutic targets—underscores their importance in both radiobiology and clinical oncology. Our research indicates that future research aimed at elucidating the molecular mechanisms of ion channel regulation under radiation exposure will be crucial for developing

new strategies to increase the effectiveness of radiotherapy while reducing its potential side effects. Additionally, the discovery of ion channel blockers and the development of new radioprotective drugs are expected to make it possible to reduce the side effects of radiotherapy.

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