Journal of Cancer and Tumor International

Volume 15, Issue 1, Page 24-37, 2025; Article no.JCTI.129422
ISSN: 2454-7360

The Role of Bioelectric Signals in Cancer Genome Regulation and Potential Therapeutic Implication: An Overview

Lawrence John Ajutor [a*], Fatima Bello Sani [b], Elijah Nehemiah Kama [c], Kingsley Ugonna Ugoagwu [d], Adegbesan Abiodun Christopher [e], Daniel Temiloluwa Oyedemi [f], Peter Bemigho Adewoyin [g], Olayinka Esther Agbetanmije [h], Adepeju Matilda Adekoya [i] and Erere Godsent Onyeugbo [j]

[a] Department of Medical Laboratory Science, University of Benin, Benin City, Edo Sate, Nigeria.
[b] Laboratory Services, Yobe State University Teaching Hospital, Damaturu, Yobe state, Nigeria.
[c] Laboratory Services, Federal University of Health Science Teaching Hospital, Azare Bauchi State, Nigeria.
[d] Department of Immunology, College of Medicine, University of Ibadan, Nigeria.
[e] Department of Global Health, African Cancer Institute, Stellenbosch University, Cape Town, South Africa.
[f] Department of Emergency Medicine, Warrington and Halton NHS Foundation Trust, England.
[g] Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.
[h] Department of Microbiology, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.
[i] Department of Cell Biology and Genetics, University of Lagos, Lagos Nigeria.
[j] Department of Medical Radiography and Radiological Sciences, University of Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jcti/2025/v15i1280

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/129422

**Corresponding author: Email: lawrenajutor@gmail.com;*

Cite as: *Ajutor, Lawrence John, Fatima Bello Sani, Elijah Nehemiah Kama, Kingsley Ugonna Ugoagwu, Adegbesan Abiodun Christopher, Daniel Temiloluwa Oyedemi, Peter Bemigho Adewoyin, Olayinka Esther Agbetanmije, Adepeju Matilda Adekoya, and Erere Godsent Onyeugbo. 2025. "The Role of Bioelectric Signals in Cancer Genome Regulation and Potential Therapeutic Implication: An Overview". Journal of Cancer and Tumor International 15 (1):24-37. https://doi.org/10.9734/jcti/2025/v15i1280.*

Review Article

Received: 05/11/2024
Accepted: 10/01/2025
Published: 16/01/2025

ABSTRACT

Bioelectrical signals which are directed by ion channels and membrane potential (V_mem), play a crucial role in many cellular processes including proliferation and differentiation. It has also been known to influence processes such as gene expression, epigenetics, and tumor progression which are key aspects of cancer development. This study explores the role of bioelectric signaling in oncogenesis, highlighting possible therapeutic implications. An inferential review of existing literature was done to understand the possible outcomes of integrating Tumor-Treating Fields (TTFields) with traditional therapies like chemotherapy and immunotherapy. Relevant sources were analyzed to gain mechanistic insights from clinical and non-clinical studies to deduce potential therapeutic implications.

Dysregulated ion channel activity and abnormal cellular membrane potential are hallmark findings of cancer cells. Deviant bioelectric signals seen in tumors promote oncogene activation and tumor suppressor silencing. These bioelectric changes affect chromatin remodeling through pathways involving calcium signaling, histone modifications, and DNA methylation.

Therapeutically, targeting ion channels, such as potassium and sodium-proton exchangers may offer a novel strategy to disrupt tumor growth. Bioelectric stimulation, using techniques like optogenetics, can also help reprogram cancer cells to induce differentiation or apoptosis. There are also potential diagnostic advancements that leverage bioelectric markers, such as depolarized membrane potential, for early cancer detection through electrophysiological imaging and wearable sensors. Bioelectric modulation can enhance drug uptake, improve immune responses by normalizing the tumor microenvironment, and enable targeted delivery using electroporation.

Bioelectrical signals influence genome regulation and offer significant therapeutic and diagnostic potential. Further studies are recommended to provide essential insights into the potential of harnessing bioelectricity for advanced cancer management and improved patient outcomes.

Keywords: Bioelectrical signals; cancer genome regulation; membrane potential; ion channels; epigenetics; cancer therapy.

LIST OF ABBREVIATIONS

BRCA1 : Breast Cancer Type 1 Susceptibility Gene
CTLA-4 : Cytotoxic T-Lymphocyte-Associated Protein 4
CYR61 : Cysteine-Rich Angiogenic Inducer 61
DNA : Deoxyribonucleic Acid
DNMTs : DNA Methyltransferases
EMT : Epithelial-to-Mesenchymal Transition
HDACs : Histone Deacetylases
HR : Homologous Recombination
K_v10.1 : Voltage-Gated Potassium Channel 10.1
KRAS : Kirsten Rat Sarcoma Virus Oncogene
Kv : Voltage-Gated Potassium Channel
MET : Mesenchymal Epithelial Transition Oncogene
MYC : Myelocytomatosis Oncogene
Na^+/H^+ Antiporters : Sodium-Proton Exchangers
Na^+/K^+ ATPase : Sodium-Potassium Pump (Adenosine Triphosphatase)
Nav : Voltage-Gated Sodium Channel
NHEJ : Non-Homologous End Joining
PD-1 : Programmed Death-1
PI3K : Phosphoinositide 3-Kinase

PRCs : Polycomb Repressive Complexes
PTEN : Phosphatase and Tensin Homolog
RB1 : Retinoblastoma 1
RNA : Ribonucleic Acid
ROS : Reactive Oxygen Species
SNAIL : Zinc Finger Protein SNAI1
TME : Tumor Microenvironment
TP53 : Tumor Protein P53
TRPV : Transient Receptor Potential Vanilloid
TWIST : Twist Family BHLH Transcription Factor
V_mem : Membrane Potential
Vmem : Transmembrane Potential
WHO : World Health Organization
YAP/TAZ : Yes-Associated Protein / Transcriptional Coactivator with PDZ-Binding Motif

1. INTRODUCTION

A common goal of oncology is to better understand the mechanisms and factors involved in cancer development. This will help to further derive novel approaches to combating the disease. Cancer is a multidimensional disease characterized by uncontrolled cell division, uncontrolled cell growth, and the ability to spread to surrounding tissues or organs (Payne et al., 2019). According to the World Health Organization (WHO), cancer is a leading cause of death worldwide, and it accounted for nearly 10 million deaths in the year 2020, or nearly one in six deaths (Tuszynski, 2019). The most common cancers known include: breast cancer, lung cancer, colon cancer, rectum, and prostate cancers (Davalos and Esteller, 2023; WHO, 2024).

Studies widely reveal that the underlying mechanisms involved in cancer development involve an interplay of genetic and epigenetic alterations (Ilango et al., 2020). Such genetic alterations in cells can involve mutations, deletions, or other alterations in the nucleotide sequences of DNA, which consist of purine (adenine and guanine) and pyrimidine (cytosine and thymine) bases. While some genetic changes may be inheritable, others occur in somatic cells and are not passed on to offspring. These alterations disrupt oncogenes and tumor suppressor genes. They also affect regulatory pathways that control cell proliferation and cell survival (Park and Han, 2019). For instance, mutations in some genes like TP53, KRAS, and BRCA1 have been frequently implicated in tumorigenesis and are found to play a higher role in cancer development. More so, other genetic factors such as chromosomal instability and aneuploidy further aggravate the genetic background of tumor cells (Davalos and Esteller, 2023).

Another equally crucial aspect of cancer development that has been described in studies is epigenetic modifications. Epigenetic modifications may also be heritable changes in gene expression that do not involve alterations in the DNA sequence. Such changes include DNA methylation, histone modifications, and the regulation of non-coding RNAs. Each modification has a way of affecting the gene expression pathways (Payne et al., 2019). For example, aberrant DNA methylation can lead to the silencing of tumor suppressor genes. When tumor suppressor genes are silenced, cells can grow and divide uncontrollably, which can lead to cancer. Changes in histone acetylation as a form of histone protein modification may disrupt cellular chromatin architecture and allow abnormal gene expression patterns to occur. Together, these genetic and epigenetic alterations form the core basis of cancer. In conjunction with other factors like sustained proliferative signaling, resistance to apoptosis, angiogenesis, and immune evasion (Park and Han, 2019).

Despite massive and impressive research efforts made over the past several decades, a full molecular understanding of cancer remains a major challenge, as cancer heterogeneity continues to defy the development of effective therapies. Consequently, several interdisciplinary approaches, such as the study of cell bioelectricity, are emerging as promising avenues to provide novel insights and innovative therapeutic strategies in cancer biology (Tuszynski, 2019).

Bioelectricity refers to the electrical phenomena generated by biological processes in living cells. Through this electrical phenomenon, intercellular and intracellular communication is made possible in a process known as bioelectric signaling. It is

an important aspect of cellular activities such as neural communication, muscle contraction, and even cell developmental processes (Payne et al., 2019). Bioelectric signals are generated through the activity of ion channels, transporters, and pumps within the cellular membrane space in the body. These electrical signals are often quantified as transmembrane potential (Vmem) (Park and Han, 2019). The establishment of transmembrane potential gradients is a result of ionic influx and efflux. It is noteworthy that the whole process involves specific ions including sodium (Na^+), potassium (K^+), chloride (Cl-), and calcium ($Ca2^+$) and everything is regulated on cellular membranes by ion channels and transport proteins which are actively present on cells (Tuszynski, 2019).

When the cytoplasm is more positively charged compared to the extracellular space, the cell is considered depolarized and exhibits a less negative Vmem. Conversely, when the cytoplasm becomes more negatively charged relative to the extracellular space, the cell is said to be hyperpolarized and has a more negative Vmem. In the context of tissue homeostasis, bioelectricity is described as overseeing critical processes such as cell proliferation, cell differentiation, cell migration, and apoptosis. These processes are tightly coordinated by bioelectrical signals that operate within individual cells and across cellular networks. For example, during embryonic development, gradients of transmembrane potential influence pattern formation and organogenesis by directing the spatial and temporal behavior of cells (Levin, 2021).

In cancer, recent studies have highlighted the role of bioelectricity in maintaining tissue architecture and preventing tumorigenesis. Most studies have associated the onset of malignancies with disruptions in transmembrane potential gradients, which are often caused by the dysregulation of ion channels (Levin, 2021). For instance, depolarized transmembrane potential states in cells have been correlated with increased proliferation and a loss of differentiation. These are notable features of cancer cells. It goes to show the importance of electrical signals not only in normal physiological contexts but also in pathological conditions such as cancer (Carvalho, 2021; Davalos and Esteller, 2023).

Knowledge of the bioelectric signals in cancer can offer a unique perspective on the disease. It can also potentially bridge the gap between cellular biophysics and molecular biology. Such a combined interdisciplinary approach can prospectively uncover novel mechanisms of tumorigenesis and identify bioelectric markers for early diagnosis and prognosis (Levin, 2021). Furthermore, studying the bioelectric properties of cancer cells can potentially add to the growing knowledge as a therapeutic strategy, offering an innovative avenue to complement already existing but limited treatments in terms of efficacy for long-term cancer (Davalos and Esteller, 2023). This review aims to explore the emerging

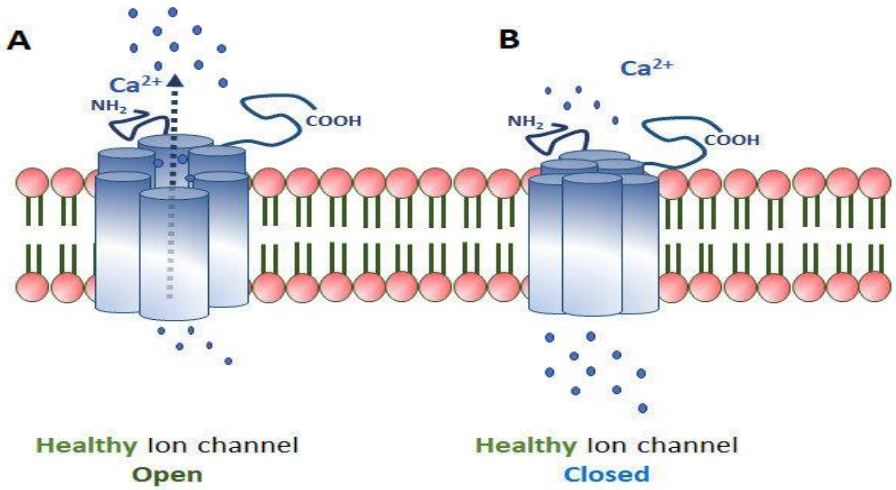

Fig. 1. Iron gated channels on the surface of cell membranes (A) An ion channel is open, allowing the flow of Ca $^{2+}$ ions, (B) A closed ion channel limiting the flow of ions (Kabra and Pattnaik, 2020)

role of bioelectrical signals in cancer genome regulation and their potential therapeutic implications. We will examine how bioelectricity intersects with genetic and epigenetic mechanisms in cancer and discuss the translational potential of bioelectric-based interventions in oncology (Levin, 2021; Davalos and Esteller, 2023).

2. BASICS OF BIOELECTRICAL SIGNALS IN CELLULAR BIOLOGY

Bioelectricity refers to the electrical properties and signaling of living cells and tissues. It generally refers to the electric potentials and currents produced by or occurring within living organisms. Bioelectric potentials are generated by a variety of biological processes and generally range in strength from 1 mV to 100 mV or more (Martinsen and Heiskanen, 2023). In modern times, the measurement of bioelectric potentials has become a routine practice in clinical medicine. For example, electrical effects originating in active cells of the heart and the brain are commonly monitored and analyzed for diagnostic purposes (Moreddu, 2024).

Bioelectric potentials may be identical to the potentials produced by devices such as batteries or generators. In nearly all cases, however, a bioelectric current consists of a flow of ions (i.e., electrically charged atoms or molecules), whereas the electric current used for lighting, communication, or power is a movement of electrons. In living cells, there is a bioelectric potential, also known as the resting potential. This is typically about 50 millivolts across a cell membrane (Martinsen and Heiskanen, 2023). All cells use their bioelectric potentials to assist or control metabolic processes. However, it is known that some cells make specialized use of bioelectric potentials and currents for distinctive physiological functions. Examples of such uses are found in nerve and muscle cells. Information is carried by electric pulses, which are called action potentials, that pass along nerve fibers (Sarada, 2022; Kofman and Levin, 2024). Similar pulses in muscle cells are seen in muscular contraction. In nerve and muscle cells, chemical or electrochemical stimulation results in temporary changes in the permeability of cell membranes, allowing the electric potential between the inside and outside to discharge as a current that is propagated along nerve fibers or activates the contractility of muscle fibers (Zhao et al., 2022).

2.1 Ion Channels and Membrane Potentials and How Human Cells Generate Electricity

Bioelectric signals are generated in human cells through the coordinated action of transmembrane proteins embedded in the plasma membrane. The membrane proteins function as ion channels, pumps, and transporters that regulate the movement of ions, such as sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}), across the lipid bilayer. Other charged molecules are also involved in this process (George and Bates, 2022). These ions have been discussed in many reviews as being able to traverse the narrow, selectively permeable pores of the membrane. When these ions pass through, an electrical gradient is generated that gives rise to the transmembrane potential. Living cells retain the ability to control the movement of these ions through the voltage-gated cell membranes. The transmembrane potential, or membrane potential (Vmem), plays a part in different cellular functions, such as the transmission of electrical signals in excitable cells like neurons and muscle fibers, as well as the regulation of key cellular processes in non-excitable cells (Sarada, 2022; Kofman and Levin, 2024).

The generation and maintenance of bioelectric signals are primarily driven by the sodium-potassium pump (Na^+/K^+ ATPase). This is categorically a kind of active transporter that plays a central role in maintaining ion gradients. The channels sit within the cell membrane to carry out this function. This pump exchanges three sodium ions (Na^+) out of the cell for two potassium ions (K^+) into the cell, consuming ATP to fuel the process (Singh et al., 2022). Thus, the sodium-potassium pump creates an intracellular environment that is slightly negatively charged when compared to the extracellular space. It is the difference in the concentration of different charged molecules that gives rise to a typical transmembrane potential (Husar and Gašpar, 2023).

George and Bates (2022) reviewed that all cells have a resting membrane potential, but the exact value of this Vmem may vary by cell type. In general, differentiated cells are hyperpolarized relative to stem cells. The generated membrane potential is rapid in some cells like neurons. In this case, it is referred to as an action potential. Studies also noted that the changes in the value of Vmem are relatively dependent on the efflux

and influx of ions (Zeise, 2021; George and Bates, 2022).

2.2 Role of Ions in Bioelectric Signals

It is crucial to discuss the role of active ion channels in bioelectric signalling. Without active ion exchange, cells may not be able to maintain the electrical gradients necessary for their function. Ion channels further refine the membrane potential by facilitating the passive movement of ions along their concentration gradients (George and Bates, 2022). These channels include voltage-gated, ligand-gated, and mechanosensitive types. The gated channels open in response to specific stimuli, such as changes in voltage, binding of signaling molecules, or mechanical forces. By allowing ions to flow freely in or out of the cell, ion channels contribute to rapid fluctuations in the membrane potential (Funk and Scholkmann, 2023).

Calcium ions (Ca^{2+}) play a role in bioelectric signalling. Calcium pumps and calcium transporters include the plasma membrane Ca^{2+}-ATPase (PMCA) and sodium-calcium exchangers which regulate intracellular calcium levels. Additionally, a very low concentration must be maintained in cells (cytoplasm) relative to the extracellular space. This tight regulation is very vital because small changes in calcium levels can have profound effects on cellular processes such as signal transduction, muscle contraction, and neurotransmitter release. In addition, calcium ions serve as a secondary messenger in many signaling pathways, further emphasizing their importance in cellular communication (Sarada, 2022; Kofman and Levin, 2024).

3. BIOELECTRIC SIGNALING IMPACT ON NORMAL CELLULAR FUNCTION

Electrical signals, established by differences in ion concentrations across the plasma membrane, act as key regulators of cellular activity. These gradients influence a variety of critical biological processes, ensuring proper cellular and tissue function:

3.1 Role of Electrical Gradients in Cellular Processes

Cell Polarity and Morphogenesis: Electrical gradients play a central role in establishing spatial cues that form cell polarity. Polarity is essentially the asymmetric distribution of cellular components that is important for processes such as embryonic development, organogenesis, and tissue repair. By creating localized electric fields, bioelectric signaling coordinates the orientation and positioning of cells within a tissue. This mechanism is very critical during morphogenesis. It is what guides cell shape and migration to form complex tissue structures. In wound healing for example, disrupted transmembrane potentials generate bioelectric cues that re-establish polarity, promoting the migration of epithelial cells to close the wound and restore tissue integrity (Jones and Larkin, 2021).

Cellular Communication: Bioelectric fields facilitate intercellular communication to consequently enable synchronized cellular responses through gap junctions, ion fluxes, and electrochemical signaling. Gap junctions are composed of connexin proteins and form channels that allow direct ion and small molecule exchange between adjacent cells (Bhavsar et al., 2020; Cheng et al., 2021). These electrical signals ensure coordinated cellular behaviors during processes such as tissue regeneration, where spatial and temporal alignment of cellular responses is critical for functional recovery. Bioelectric signaling also plays a part in specific biochemical pathways to modulate cellular decision-making and tissue-level organization (Cheng et al., 2021).

Regulation of Gene Expression: Electrical gradients influence gene expression through their effects on transmembrane potential (Vmem) and chromatin organization. This will be discussed in more detail later in this paper. Changes in Vmem can alter intracellular signaling pathways, such as calcium-mediated processes, which regulate transcription factors and chromatin accessibility (Jones and Larkin, 2021; Bhavsar et al., 2020). For instance, hyperpolarization of Vmem has been linked to the activation of differentiation-specific genes in stem cells, driving lineage commitment and specialized tissue formation. Similarly, depolarized states may suppress genes associated with quiescence or differentiation, highlighting the dual regulatory role of bioelectric signals in cellular programming (Bhavsar et al., 2020).

Control of Ion Homeostasis: Electrical gradients are required for the maintenance of ion homeostasis for cellular function and survival. Ion channels and pumps regulate the intracellular

concentrations of critical ions, such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-), which influence processes including intracellular pH regulation, osmotic balance, and mitochondrial bioenergetics. Disruptions in ion gradients can impair metabolic activity, redox balance, and organelle function, leading to cellular dysfunction. Proper ion homeostasis is also important in excitable tissues, such as neurons and myocytes, where rapid changes in electrical gradients strengthen signaling and contractile activity (Carvalho, 2021).

Wound Healing and Regeneration: Bioelectric fields carry specific signatures, and when tissues are damaged, these signatures undergo dramatic shifts. During tissue injury, the disruption of electrical gradients generates endogenous electric fields that serve as directional cues for cell migration, a process known as electrotaxis (Fontani et al., 2023). Epithelial and mesenchymal cells detect these bioelectric signals and migrate toward areas of injury, facilitating wound closure and tissue regeneration. In addition to guiding cell movement, electrical gradients regulate the expression of genes involved in cell proliferation, matrix remodeling, and angiogenesis. This bioelectric regulation ensures that tissue repair processes are spatially and temporally coordinated (Buchanan and Vandier, 2022).

3.2 Influence of Bioelectric Signals on Cellular Growth

Electrical signals may vary across different cell types. Overall, it has been established that they play a role as crucial regulators of key cellular processes such as proliferation, differentiation, and migration. Although reports have been mostly experimental, the transmembrane potential (Vmem) serves as a bioelectric cue that directs these processes (Husar and Gašpar, 2023).

Many studies have reported fluctuations in Vmem values in cell proliferation and cell cycle progression. Depolarized Vmem states promote mitotic activity, particularly in progenitor and stem cells, enabling tissue growth and repair. Hyperpolarization, on the other hand, may be associated with quiescent or terminally differentiated states. Evidently, modern reviews show the role of bioelectric signals in supporting cell division.

Bioelectric signals may also have a hand in influencing lineage commitment by modulating intracellular signaling cascades and gene expression. Zhu et al. (2024) noted that hyperpolarization of specific membrane potentials may affect the activation of differentiation-specific transcription factors. Contextually, RUNX2 in osteoblasts or PAX6 in neural progenitors may play roles in enabling the transition of stem cells into specialized cell types. In addition, some experimental shifts in ion gradients, such as increased intracellular calcium levels, activate signaling pathways like the Notch and Wnt pathways, further reinforcing differentiation (Zhu et al., 2024).

On another note, the process of directed cell migration, known as electrotaxis, in response to electric fields, is quite critical to tissue repair and development. Electrical gradients form electrical signaling that is generated by ion fluxes via cell membrane channels like ENaC and TRP family channels, guiding cells to specific locations during wound healing and tissue patterning (Husar and Gašpar, 2023; Zhu et al., 2024). Changes in Vmem can also influence cytoskeletal dynamics by regulating actin polymerization and focal adhesion assembly through Rho-GTPase pathways. This ensures precise migratory behavior, as seen in keratinocytes and fibroblasts during wound closure, where they align and migrate toward the wound site in response to local electric fields (Zhu et al., 2024).

3.3 Bioelectric Cues in Maintaining Genomic Stability

Bioelectric signals are integral to preserving genomic stability. They act as regulators of DNA integrity, chromatin architecture, and intracellular signaling pathways. Bioelectric signals orchestrate ion homeostasis, which in turn influences calcium dynamics, reactive oxygen species (ROS) generation, and cellular stress responses, all of which are critical elements for maintaining genome fidelity (Husar and Gašpar, 2023). Electrical gradients help to regulate chromatin dynamics by altering transmembrane potentials, which can also influence epigenetic modifications (Husar and Gašpar, 2023). Such effects could be beneficial in normal cell dynamics. Hyperpolarized membrane states, which are more negative, have often correlated with a more stable chromatin structure that suppresses transcriptional noise and reduces susceptibility to DNA damage. For instance, calcium-dependent chromatin remodeling

enzymes are modulated by bioelectric signals, reinforcing the role of ion homeostasis in genome protection.

Stress Response and DNA Repair are processes that spontaneously occur in living cells. Bioelectric signals have been known to influence key aspects of cellular responses to genotoxic stress and mediate pathways responsible for DNA repair. Intracellular calcium fluxes, which are majorly regulated by electrical gradients, activate repair mechanisms such as homologous recombination (HR) and non-homologous end joining (NHEJ). The electrical regulation of ionic homeostasis ensures a finely tuned balance between repair activation and ROS mitigation (Sarada, 2022; Kofman and Levin, 2024).

Also, in mitotic regulation, proper mitosis relies on bioelectric signals to coordinate spindle formation, chromosomal segregation, and cytokinesis. Electrical gradients regulate the activity of ion channels that control microtubule and centrosome function (Jones and Larkin, 2021; Robinson et al., 2021).

4. BIOELECTRIC SIGNALLING IN CANCER GENOME REGULATION

The bioelectric state of cancer cells is different from that of healthy cells, causing a disruption in the cellular signaling pathways. Deviant expression and function of ion channels are typically seen in cancer progression and this alter the membrane potential (V_mem), causing a deviation in the normal cellular homeostasis, and the regulation of oncogenic pathways (Zhao et al., 2022).

4.1 Alterations in Bioelectric Signaling in Cancer Cells

Cancer cells frequently exhibit disrupted bioelectric signaling due to the misregulation of ion channels and transporters. These disruptions manifest as abnormal shifts in membrane potential (V_mem) and it changes cells from a typically polarized or hyperpolarized state to a depolarized phenotype. This depolarization is implicated in promoting hallmark behaviors of cancer. Depolarization affect intricate cellular processes like uncontrolled proliferation, evasion of apoptosis, and metastasis. Dysregulated bioelectric signaling is known to modulate key transcriptional programs, thereby influencing the expression of genes (Riol et al., 2021). Aberrant ion channel activity is a consequence and a driver of oncogenesis. Specific ion channels, such as voltage-gated potassium channels (e.g. K_v10.1), chloride channels, and sodium-proton exchangers, have been identified as critical mediators of cancer progression (Zeise, 2021).

Ion channels can be classified into voltage-gated and ligand-gated types. Advances in molecular techniques have facilitated a more detailed classification based on subunit type and gating mechanisms, including physical factors (light, temperature, pressure, and tonicity), chemical factors (pH, pO_2), and intracellular factors (ATP, secondary messengers).

It is now recognized that numerous ion channels exhibit dysregulated expression in cancer cells, often correlating with a metastatic phenotype. For instance, microarray expression profiling of ion channel genes in patient with primary tumors of breast cancer, lung and adenocarcinoma, has revealed significant differential expression compared to normal tissues. Additionally, publicly available gene expression datasets, such as those on platforms like cBioPortal, Oncomine, or the Broad CCLE portal, are providing further insights to ion expression profiles in various cancers (Zeise, 2021).

4.2 Influence of Bioelectric Signals on Gene Expression and Epigenetics

Bioelectric signaling has profound implications for gene expression and epigenetic regulation. It influences the activation or repression of oncogenes and tumor suppressor genes, ultimately shaping cancer development and progression (Harris, 2021).

4.2.1 Mechanisms linking electrical signals to chromatin remodeling

In cancer cells, bioelectric signals initiate intracellular signaling cascades that modulate chromatin architecture. These mechanisms involve changes in V_mem which alter the flow of calcium ions (Ca^{2+}) which is a key second messenger involved in chromatin remodeling. Elevated intracellular Ca^{2+} levels activate calcium-dependent enzymes such as histone deacetylases (HDACs) and protein kinases, which modify histones and influence chromatin accessibility. These modifications facilitate cancer progression (Harris, 2021).

4.2.2 Electrochemical gradients and epigenetic modulators

Variations in V_mem impact electrochemical gradients across the nuclear envelope,

influencing the nuclear import and export of transcription factors and chromatin remodelers. For example, changes in potassium ion (K^+) concentrations regulate the activity of polycomb repressive complexes (PRCs) that mediate histone methylation, thereby controlling gene silencing.

4.2.3 Voltage-gated ion channels and DNA methylation

Ion channel activity modulates the expression of DNA methyltransferases (DNMTs), enzymes responsible for adding methyl groups to CpG islands in gene promoters. Dysregulation of V_mem during cancer progression may lead to aberrant methylation patterns, resulting in the silencing of tumor suppressor genes or the activation of oncogenes (Masuelli et al., 2022).

4.3 Role in Regulating Oncogenes and Tumor Suppressor Genes

4.3.1 Oncogene activation

Depolarized membrane potential (Vmem) in cancer cells facilitates the activation of oncogenes such as MYC, RAS, and MET. This depolarization has been shown to trigger alterations in chromatin structure, enhancing accessibility to the promoter regions of these genes. Specifically, ion channel-regulated transcription factors like NF-κB and AP-1 may also be activated, leading to the transcriptional upregulation of oncogenes (Anderson, 2024). All these contribute to cellular processes that promote uncontrolled proliferation, survival, and metastasis. The ability of depolarized Vmem to alter chromatin dynamics underscores the direct relationship between bioelectric signals and the activation of oncogenic pathways (Liszewski et al., 2024).

4.3.2 Tumor suppressor gene silencing

While hyperpolarization typically maintains the activity of tumor suppressor genes, depolarization of the membrane potential results in the silencing of critical tumor suppressor genes like TP53, RB1, and PTEN. This repression occurs through epigenetic modifications, particularly hypermethylation and histone deacetylation. More so, depolarization can activate the upregulation of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), which catalyze the silencing of these genes. As a result, tumor suppressor functions are lost, allowing for unchecked cell growth and evasion of apoptosis. The bioelectric alterations that lead to tumor suppressor gene silencing play a pivotal role in cancer initiation and progression (Srivastava et al., 2021).

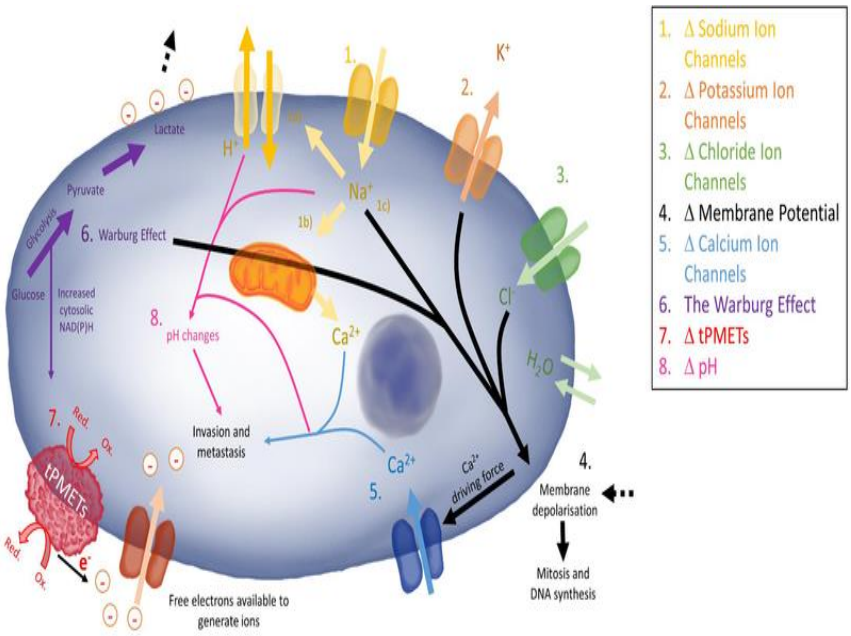

Fig. 2. Complex bioelectrical signalling in cancer cells showing dysregulated ion channel and changes in ion regulation leading to depolarized membrane potential (Robinson et al., 2021)

4.3.3 Control of EMT and stemness pathways

Bioelectric signals also regulate the expression of transcription factors associated with the epithelial-to-mesenchymal transition (EMT) and cancer stem cell phenotypes. These factors, such as TWIST, SNAIL, and OCT4, are involved in maintaining stemness and promoting metastasis. Bioelectric signals influence chromatin remodeling complexes like BRG1 and the SWI/SNF complex, which are essential for the transcriptional reprogramming that underlies EMT and the acquisition of metastatic properties. Furthermore, the modulation of ion channels by bioelectric signals affects cellular plasticity, allowing cancer cells to transition between different phenotypic states. These changes contribute to therapy resistance and the ability of cancer cells to invade surrounding tissues (Masuelli et al., 2022).

5. BIOELECTRIC SIGNALS AS POTENTIAL TARGETING OPPORTUNITIES FOR CANCER THERAPY

5.1 Targeting Electrical Signals for Cancer Therapy

5.1.1 Modulation of ion channels as a therapeutic strategy

Given the current understanding of the role of bioelectricity in cancer, modulating bioelectric signaling can help as an innovative frontier in cancer therapy. One way is to further probe the role of ion channels and membrane potential (V_mem) as therapeutic targets. Ion channels are crucial mediators of cellular bioelectricity which have been shown to influence oncogenic pathways, making them a potential target for malignancy intervention (Schofield et al., 2020). For example, voltage-gated potassium channels like K_v10.1 in cell membranes are reportedly overexpressed in several malignancies. By selectively targeting such ion channels with drugs such as amiodarone (a potassium channel blocker) and verapamil (a calcium channel blocker), it is possible to disrupt the bioelectric signaling networks that sustain malignant proliferation. In another aspect, inhibiting sodium-proton exchangers (e.g., Na^+/H^+ antiporters) using drugs such as Amiloride could normalize the pH of the tumor microenvironment, reducing its permissiveness for tumor growth and metastasis (Singh et al., 2022; Moreddu, 2024). The goal of such processes can be to restore polarization.

5.1.2 Use of bioelectric stimulation for reprogramming cancer cells

Beyond pharmacological approaches, bioelectric stimulation has gained attention of researchers as a strategy to reprogram cancer cells by restoring normal membrane potential. This approach capitalizes on the plasticity of cancer cells, this can induce differentiation or apoptosis (Schofield et al., 2020). Techniques such as electrical stimulation therapy apply low-frequency electrical currents to modulate ion channel activity, influencing intracellular signaling cascades that regulate cell fate (Levin, 2021; Anderson, 2024). Furthermore, advances in optogenetics and electrogenetics which are technologies that allow precise control of ion channel activity via light or electric fields have shown promise in reversing malignant bioelectri phenotypes in preclinical models. By reprogramming the bioelectric landscape of tumors, the aim is to disrupt cancer progression while minimizing harm to normal cells (Levin, 2021; Anderson, 2024).

However, challenges remain, particularly in identifying tumor-specific bioelectric signatures and ensuring the specificity of bioelectric interventions. Despite these hurdles, the therapeutic potential of targeting bioelectric signaling continues to grow, offering a novel dimension to the fight against cancer (Anderson, 2024).

5.2 Integration of Bioelectric Modulation with Existing Cancer Therapies

Prospectively, bioelectric signal targeting could be an important addition to currently existing cancer therapies, such as chemotherapy and immunotherapy. It may turn out to be a promising avenue for enhancing therapeutic efficacy and overcoming limitations of current cancer treatments.

5.2.1 Enhancing chemotherapy through bioelectric modulation

Chemotherapy currently has widespread use, but faces significant challenges, including drug resistance and non-specific toxicity. Bioelectric modulation offers strategies to enhance drug efficacy by sensitizing cancer cells to chemotherapeutic agents (Schofield et al., 2020; Moreddu, 2024). For instance, restoring hyperpolarized membrane potential (V_mem) in cancer cells can induce a pro-apoptotic state,

making them more susceptible to drugs like cisplatin and doxorubicin. Moreover, bioelectric pulses, such as those used in electroporation, temporarily increase cell membrane permeability. This facilitates the uptake of chemotherapeutics directly into cancer cells (Singh et al., 2022; Moreddu, 2024).

Beyond sensitization, bioelectric modulation can also counteract chemoresistance mechanisms. Cancer cells often evade chemotherapy by altering ion channel activity to sustain survival pathways. Targeting ion channels with specific inhibitors, alongside chemotherapy, can disrupt these protective mechanisms, forcing cancer cells into apoptosis or halting their proliferation. This dual approach has shown promise in preclinical studies (Singh et al., 2022; Moreddu, 2024).

5.2.2 Synergy with immunotherapy

Immunotherapy has revolutionized cancer treatment with an approach of strengthening the immune system through various methods, including gene editing to target tumors (Ajutor et al., 2024). However, efficacy is often limited by the immunosuppressive tumor microenvironment (TME), which is characterized by hypoxia, low pH, and nutrient deprivation. Bioelectric modulation can reshape the tumor environment. For example, reprogramming membrane potentials in cancer cells can reduce extracellular acidity, alleviating the inhibitory effects of low pH on cytotoxic T cells and natural killer cells (Schofield et al., 2020).

Additionally, bioelectric signals have been implicated in the regulation of immune checkpoint pathways. Voltage-sensitive ion channels on the membrane of immune cells influence their activation and effector functions. Thus, modulating these channels through bioelectric interventions could amplify the effectiveness of immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 therapies, enabling a more robust immune response against tumors (Singh et al., 2022; Moreddu, 2024).

5.3 Electrical Signal-Based Diagnostic Tools

Another key aspect that should be explored is the diagnostic potential of bioelectric signals, which could make them a potential early biomarker for malignancies. Cancer cells exhibit unique bioelectric profiles, often characterized by depolarized V_mem and dysregulated ion channel activity, which differentiate them from normal cells (Lee et al., 2024). These bioelectric changes precede many biochemical alterations, making them valuable for early detection. Techniques like voltage-sensitive dye imaging and bioelectric tomography can provide non-invasive ways to map specific electrical activity in tissues to help identify precancerous lesions and early-stage tumors (Liszewski, 2024).

High-resolution electrophysiological imaging can uncover spatial and temporal patterns of bioelectric abnormalities in tissues, providing insights into tumor initiation and progression. For example, clusters of depolarized cells could signal the onset of neoplastic transformation, even before morphological changes become apparent (Moreddu, 2024). This is particularly significant for cancers with high mortality rates, such as pancreatic or ovarian cancers, where early diagnosis greatly improves outcomes. Implantable or wearable bioelectric sensors are also being developed to monitor bioelectric signatures in real-time, offering a dynamic diagnostic approach that could detect recurrent tumors or assess treatment response (Singh et al., 2022; Moreddu, 2024).

Moreover, integrating bioelectric diagnostics with molecular and imaging techniques can enhance diagnostic accuracy. For instance, combining bioelectric profiling with biomarkers like circulating tumor DNA or MRI imaging could provide a comprehensive view of tumor biology (Singh et al., 2022; Moreddu, 2024). Despite these advances, further research is required to standardize bioelectric diagnostic criteria and address technical challenges such as signal interference and resolution limits (Huang et al., 2024).

5.4 Improving Drug Delivery and Precision

The use of bioelectric fields to enhance drug delivery is another area of integration. Electroporation, for instance, can direct both chemotherapeutic agents and immunostimulatory compounds to specific tumor regions, ensuring higher local concentrations while minimizing systemic side effects (Singh et al., 2022; Moreddu, 2024). This precision reduces toxicity and enhances therapeutic effectiveness. Furthermore, bioelectric stimulation can activate drug-delivery systems such as nanoparticles,

which release their payload only in response to specific electrical signals, providing a highly targeted treatment approach (Shrivastava et al., 2024).

7. CONCLUSION

Bioelectrical signals play a pivotal role in cancer genome regulation, influencing gene expression, epigenetics, and key oncogenic pathways. Dysregulated ion channel activity and membrane potential drive tumor progression by promoting EMT, angiogenesis, and immune evasion. Therapeutic strategies targeting ion channels and bioelectric stimulation offer promising avenues to reprogram cancer cells and enhance existing therapies like chemotherapy and immunotherapy. Diagnostic advancements using bioelectric markers are also promising consideration to enable early cancer detection and precise monitoring. Overall, harnessing bioelectricity provides has great potential to transform current approach to cancer management. Although further continuous studies are required with significant potential to improve therapeutic outcomes and patient care.

7. RECOMMENDATION

Rigorous clinical trials are needed to evaluate the efficacy and safety of ion channel modulators and bioelectric stimulation in combination with conventional therapies. Future research should prioritize personalized bioelectric therapies tailored to the specific bioelectric profiles of individual tumors. Investigating novel bioelectric modulation technologies, such as optogenetics and nanoparticle-based approaches, could enhance therapeutic precision. Future research should examine the interplay between bioelectric signals and immune responses in specific cancer types and/or subtypes

8. LIMITATIONS OF THE STUDY

While this study provides an overview of bioelectric signals in cancer genome regulation, it may not comprehensively address the heterogeneity of bioelectric mechanisms across all cancer types. The review heavily relies on existing literature, and experimental validation of certain hypotheses, such as specific ion channel-targeted therapies, may be limited. Many findings discussed are based on preclinical studies, which may not directly translate to clinical outcomes.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Ajutor, L. J., Agbo, O. S., Adobor, C. A., Iyoyojie, B. A., Ugoagwu, K. U., Manawa, O., Faluyi, O., Ismaila, E. O., Ugwuanyi, O. E., & Adekoya, A. M. (2024). Gene Editing in Cancer Immunotherapy: Mechanisms, Advancements, Limitations and Future Directions. *Asian Journal of Biochemistry, Genetics and Molecular Biology*, *16*(12), 121–135. https://doi.org/10.9734/ajbgmb/2024/v16i12428

Anderson, B. (2024). Bioelectricity: A top-down control model to promote more effective aging interventions. *Bioelectricity, 6*(1), 2–12. https://doi.org/10.1089/bioe.2024.001

Bhavsar, M. B., Leppik, L., Costa Oliveira, K. M., & Barker, J. H. (2020). Role of bioelectricity during cell proliferation in different cell types. *Frontiers in Bioengineering and Biotechnology, 8,* 603. https://doi.org/10.3389/fbioe.2020.00603

Buchanan, P. J., & Vandier, C. (2022). Bioelectricity of the tumor microenvironment. *Bioelectricity, 4*(2), 73–74. https://doi.org/10.1089/bioe.2022.002

Carvalho, J. (2021). A bioelectric model of carcinogenesis, including propagation of cell membrane depolarization and reversal therapies. *Scientific Reports, 11*(1), 13607. https://doi.org/10.1038/s41598-021-93157

Cheng, H., Huang, Y., Yue, H., & Fan, Y. (2021). Electrical stimulation promotes stem cell neural differentiation in tissue engineering. *Stem Cells International, 2021*(1),

6697574. https://doi.org/10.1155/2021/6697574

Davalos, V., & Esteller, M. (2023). Cancer epigenetics in clinical practice. *CA: A Cancer Journal for Clinicians, 73*(4), 376–424. https://doi.org/10.3322/caac.21737

Fontani, V., Cruciani, S., Santaniello, S., Rinaldi, S., & Maioli, M. (2023). Impact of REAC regenerative endogenous bioelectrical cell reprogramming on MCF7 breast cancer cells. *Journal of Personalized Medicine, 13*(6), 1019. https://doi.org/10.3390/jpm13061019

Funk, R. H., & Scholkmann, F. (2023). The significance of bioelectricity on all levels of organization of an organism. Part 1: From the subcellular level to cells. *Progress in Biophysics and Molecular Biology, 177,* 185–201. https://doi.org/10.1016/j.pbiomolbio.2023.05.004

George, L. F., & Bates, E. A. (2022). Mechanisms underlying influence of bioelectricity in development. *Frontiers in Cell and Developmental Biology, 10,* 772230. https://doi.org/10.3389/fcell.2022.772230

Harris, M. P. (2021). Bioelectric signaling as a unique regulator of development and regeneration. *Development, 148*(10), dev180794. https://doi.org/10.1242/dev.180794

Huang, Y., Yao, K., Zhang, Q., Huang, X., Chen, Z., Zhou, Y., & Yu, X. (2024). Bioelectronics for electrical stimulation: Materials, devices and biomedical applications. *Chemical Society Reviews.* https://doi.org/10.1039/D4CS00123A

Husar, P., & Gašpar, G. (2023). Origin and detection of bioelectric signals. In *Electrical Biosignals in Biomedical Engineering: Medical Sensors, Measurement Technology and Signal Processing* (pp. 3–26). Berlin, Heidelberg: Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-662-64767-2_1

Ilango, S., Paital, B., Jayachandran, P., Padma, P. R., & Nirmaladevi, R. (2020). Epigenetic alterations in cancer. *Frontiers in Bioscience-Landmark, 25*(6), 1058–1109. https://doi.org/10.2741/4862

Jones, J. M., & Larkin, J. W. (2021). Toward bacterial bioelectric signal transduction. *Bioelectricity, 3*(2), 116–119. https://doi.org/10.1089/bioe.2021.001

Kabra, M., & Pattnaik, B. R. (2020). Sensing through non-sensing ocular ion channels. *International Journal of Molecular Sciences*, *21*(18), 6925.

Kofman, K., & Levin, M. (2024). Bioelectric pharmacology of cancer: A systematic review of ion channel drugs affecting the cancer phenotype. *Progress in Biophysics and Molecular Biology.* https://doi.org/10.1016/j.pbiomolbio.2024.101129

Lee, H., Cho, S., Kim, D., Lee, T., & Kim, H. S. (2024). Bioelectric medicine: Unveiling the therapeutic potential of micro-current stimulation. *Biomedical Engineering Letters, 14*(3), 367–392. https://doi.org/10.1007/s13534-024-00271-6

Levin, M. (2021). Bioelectrical approaches to cancer as a problem of the scaling of the cellular self. *Progress in Biophysics and Molecular Biology, 165,* 102–113. https://doi.org/10.1016/j.pbiomolbio.2021.04.003

Liszewski, K. (2024). To reverse aging's clock, adjust the cell's machinery: Epigenetic, bioelectromic, synaptic, and senolytic interventions could rejuvenate cells and counter the effects of aging. *Genetic Engineering & Biotechnology News, 44*(10), 32–34. https://doi.org/10.1089/gen.2024.0034

Martinek, R., Ladrova, M., Sidikova, M., Jaros, R., Behbehani, K., Kahankova, R., & Kawala-Sterniuk, A. (2021). Advanced Bioelectrical Signal Processing Methods: Past, Present, and Future Approach-Part III: Other Biosignals. *Sensors (Basel, Switzerland)*, *21*(18), 6064. https://doi.org/10.3390/s21186064

Martinsen, O. G., & Heiskanen, A. (2023). *Bioimpedance and bioelectricity basics.* Elsevier. https://doi.org/10.1016/C2023-0-01915-1

Masuelli, S., Real, S., Campoy, E., Branham, M. T., Marzese, D. M., Salomon, M., De Blas, G., Arias, R., Levin, M., & Roqué, M. (2022). When left does not seem right: epigenetic and bioelectric differences between left- and right-sided breast cancer. *Molecular medicine (Cambridge, Mass.)*, *28*(1), 15. https://doi.org/10.1186/s10020-022-00440-5

Moreddu, R. (2024). Nanotechnology and cancer bioelectricity: Bridging the gap between biology and translational

medicine. *Advanced Science, 11*(1), 2304110. https://doi.org/10.1002/advs.202304110

Park, J. W., & Han, J. W. (2019). Targeting epigenetics for cancer therapy. *Archives of Pharmacal Research, 42,* 159–170. https://doi.org/10.1007/s12272-019-01174-8

Payne, S. L., Levin, M., & Oudin, M. J. (2019). Bioelectric Control of Metastasis in Solid Tumors. *Bioelectricity*, *1*(3), 114–130. https://doi.org/10.1089/bioe.2019.0013

Riol, A., Cervera, J., Levin, M., & Mafe, S. (2021). Cell systems bioelectricity: How different intercellular gap junctions could regionalize a multicellular aggregate. *Cancers, 13*(21), 5300. https://doi.org/10.3390/cancers13215300

Robinson, A. J., Jain, A., Sherman, H. G., Hague, R. J., Rahman, R., Sanjuan-Alberte, P., & Rawson, F. J. (2021). Toward hijacking bioelectricity in cancer to develop new bioelectronic medicine. *Advanced Therapeutics, 4*(3), 2000248. https://doi.org/10.1002/adtp.202000248

Sarada, M. (2022). Basics and descriptions of different biomedical signals. In *AI-Enabled Smart Healthcare Using Biomedical Signals* (pp. 1–25). IGI Global. https://doi.org/10.4018/978-1-7998-9148-1.ch001

Schofield, Z., Meloni, G. N., Tran, P., Zerfass, C., Sena, G., Hayashi, Y., Grant, M., Contera, S. A., Minteer, S. D., Kim, M., Prindle, A., Rocha, P., Djamgoz, M. B. A., Pilizota, T., Unwin, P. R., Asally, M., & Soyer, O. S. (2020). Bioelectrical understanding and engineering of cell biology. *Journal of the Royal Society, Interface*, *17*(166), 20200013. https://doi.org/10.1098/rsif.2020.0013

Shrivastava, A., Kumar, A., Aggarwal, L. M., Pradhan, S., Choudhary, S., Ashish, A., Kashyap, K., & Mishra, S. (2024). Evolution of Bioelectric Membrane Potentials: Implications in Cancer Pathogenesis and Therapeutic Strategies. *The Journal of membrane biology*, *257*(5-6), 281–305. https://doi.org/10.1007/s00232-024-00323-2

Silic, M. R., & Zhang, G. (2023). Bioelectricity in developmental patterning and size control: evidence and genetically encoded tools in the zebrafish model. *Cells*, *12*(8), 1148.

Singh, A. K., Awasthi, R., & Malviya, R. (2022). Bioelectronic medicines: Therapeutic potential and advancements in next-generation cancer therapy. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, *1877*(6), 188808.

Srivastava, P., Kane, A., Harrison, C., & Levin, M. (2021). A meta-analysis of bioelectric data in cancer, embryogenesis, and regeneration. *Bioelectricity*, *3*(1), 42-67.

Tuszynski, J. A. (2019). The bioelectric circuitry of the cell. *Brain and human body modeling: Computational human modeling at EMBC 2018*, 195-208.

World Health Organization (2024). Cancer. Retrieved December 10, 2024, from https://www.who.int/health-topics/cancer#tab=tab_1

Zeise, M. L. (2021). Electrical signals in the nervous system. *Neuroscience for Psychologists: An Introduction*, 11-47.

Zhao, M., Rolandi, M., & Isseroff, R. R. (2022). Bioelectric signaling: role of bioelectricity in directional cell migration in wound healing. *Cold Spring Harbor Perspectives in Biology*, *14*(10), a041236.

Zhu, S., Chen, W., Masson, A. *et al.* Cell signaling and transcriptional regulation of osteoblast lineage commitment, differentiation, bone formation, and homeostasis. *Cell Discov* 10, 71 (2024). https://doi.org/10.1038/s41421-024-00689-6

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/129422