Electrical Difference from Normal and Cancer Cells

https://www.sciencedirect.com/science/article/abs/pii/S157106452200063X

The distinguishing electrical properties of cancer cells 2022

Highlights

- Every cell of the human body has specific electrical properties.
- Cancer cells differ significantly in their electrical properties from normal cells.
- Cancer cells exhibit extracellular and intracellular pH alterations.
- Cancer cells have a lower transmembrane potential than normal cells and different ionic concentrations.
- Electrostatic properties of cancer cells are becoming a focus of new therapies.

Every cell in the human body possesses electrical properties that are essential for proper behaviour both within and outside of the cell itself. It is not yet clear whether these changes correlate with cell mutation in cancer cells, or only with their subsequent development.

We review four essential electrical characteristics of cells, providing a deep understanding of the electrostatic changes in cancer cells compared to their normal counterparts. In particular, we provide an overview of intracellular and extracellular pH modifications, differences in ionic concentrations in the cytoplasm, transmembrane potential variations, and changes within mitochondria.

In 1924, the Warburg hypothesis proposed that mitochondrial malfunction was the cause of tumourigenesis in cancer [2]. This was one of the first cues that diverted the focus away from genetic causes. A couple of years later, Fricke and Morse discovered that cancerous breast tissue has a greater capacitance than normal breast tissue, which inspired their novel suggestion to use the unique electrical properties of cancers as a diagnostic tool and classification parameter [3]. A new interest arose in the 1970s when C. D. Cone suggested a correlation between voltage and proliferation [4]. Since then, other hypotheses have been formulated, and new approaches to treating cancer that use pulsed or alternating electric fields (EFs) or time-varying electromagnetic fields (EMFs) have emerged.

Numerous studies have been carried out since the 1970s to employ, simulate, and investigate the use of non-ionizing (and often nonthermal) microsecond electric impulses to rupture the lipid bilayer membrane and create pores [10], [11], [12]. This process, later termed **electroporation** [13] or **electropermeabilization** [14], did not damage the lipid membrane since it involves a dielectric breakdown of the bilayer structure and has different biological effects. In oncology, four methods have been developed using electroporation as a cancer treatment: electrochemotherapy, irreversible electroporation, gene electrotransfer, and calcium electroporation.

On the other hand, many studies have demonstrated that exposing cancer cells to ELF-EMFs can suppress their proliferation [35], [40], [41], [42], [43]. Ultimately, the effects of ELF-EMFs on different cell types appear to be frequency-dependent [44].

First, we describe the effects of alterations in the intracellular and extracellular pH of cancer cells in Section 2.

Second, we discuss the changes in the intracellular and extracellular concentrations of calcium, sodium, and potassium ions in cancer cells, and the subsequent effects of such ionic changes, in Section 3. The dysfunction of ion channels in cancer cells is also discussed.

Third, we provide an overview of the changes in the transmembrane potential of cancer cells in Section 4.

Lastly, in Section 5, we describe each of these altered electrical properties (pH, ionic concentration, and membrane potential) within the mitochondria of cancer cells.

Additionally, we discuss the consequences of these distinguishing electrical properties of cancer cells in Section 6. The therapeutic considerations that arise based on the unique electrical properties of cancer cells, and the state-of-the-art of EMF-based cancer therapies, are discussed in Section 7. Concluding remarks are provided in Section 8.

https://www.nature.com/articles/s41598-017-13545-3

Dielectric imaging for differentiation between cancer and inflammation in vivo 2017

Compared to normal tissues, cancer tissues exhibit higher capacitance values, allowing us to image the cancer region and monitor the chemotherapeutic effects of cancer in real-time.

https://www.sciencedirect.com/sdfe/pdf/download/eid/1-s2.0-S1571064523001318/first-page-pdf

Electrical properties of cancer cells: A next generation biophysical therapeutic target 2023

As one example, the Warburg effect (a concept that dates as far back as the 1920's) [3] has long been recognized as a viable therapeutic target in recent years [4], and the current review expertly analyzes how this phenomenon impacts pH homeostasis and ionic changes within cancer cells, and the various downstream results of these changes [1].

Another unique modality, electric field (EF) therapy, has emerged as another viable therapy modality due to its ability to influence various electrical characteristics of cancer cells, such as intracellular pH, ion concentrations, cytoskeleton dynamics, membrane permeability, metabolism, and many others.

https://www.sciencedirect.com/science/article/abs/pii/S157106452300132X

Cancer's unique bioelectric properties: From cells to body-wide networks 2023

Cancer cells have unique electrical properties that distinguish them from normal cells.

Their paper delves deeply into four main electrical characteristics of cancer cells: the internal and external pH of the cancer cell; the changes in ion concentrations and expression of ion channels; the broader changes in membrane potential; and finally mitochondrial pH, ion channels, and membrane potential.

It is worthwhile to also note that in addition to increasing internal calcium ion concentrations, Bergandi et al. also showed that the mitochondrial respiratory chain complexes and ATP synthase were upregulated in extremely low frequency electromagnetic field stimulated (ELF-EMF) cancer cells [2].

https://www.sciencedirect.com/science/article/pii/S0167488919300941

The extremely low frequency electromagnetic stimulation selective for cancer cells elicits growth arrest through a metabolic shift 2019

Highlights

- Our thermodynamic model selects the frequency of ELF-EMF specific for each cancer.
- The specific frequency of ELF-EMF inhibits cancer cell proliferation.
- The effect of ELF-EMF is abolished by the inhibition of calcium fluxes.
- ELF-EMF induces a mitochondrial respiratory burst associated with production of ROS.
- The elicited metabolic shift makes ELF-EMF a promising personalized tumor treatment.

The efficacy of the very low frequency electromagnetic field in cancer treatment remains elusive due to a lack of explanatory mechanisms for its effect. We developed a novel thermodynamic model that calculates for every cell type the frequency capable of inhibiting proliferation.

The effect was abolished by the inhibition of calcium fluxes. We found evidences of an enhanced respiratory activity due to the increased expression of the elements of the respiratory chain and oxidative phosphorylation, both at the mRNA and protein level. The respiratory burst potentiated the production of reactive oxygen species but was not associated to increased levels of ATP, leading to the conclusion that the energy was readily spent in the adaptive response to the electromagnetic field.

The treatment significantly inhibited cell growth only at a frequency specific for each cell type, namely 6 Hz for MDA-MB-231 cells, 16 Hz for MSTO-211H and 13 Hz for HUVEC (Fig. 1). The stimulation did not affect the non-malignant counterpart.

https://www.sciencedirect.com/science/article/abs/pii/S1571064523000933

Implications of cell's electrical properties for standard of care in glioblastoma therapy 2023

This paper explains that tumor cells have an alkaline intracellular pH [1], an advantage for the treatment with TMZ(temozolomide). In contrast, normal cells have lower intercellular pH [1].

https://www.researchgate.net/publication/261360055_The_Electrical_Properties_of_Cancer_Cells

The Electrical Properties of Cancer Cells 2014

One characteristic feature of both proliferating cells and cancer cells is that these cells have cell membrane potentials that are lower than the cell membrane potential of healthy adult cells (Cone, 1975). After the repair is completed the normal cells in the area of injury stop growing and their membrane potential returns to normal. In cancerous tissue the electrical potential of cell membranes is **maintained at a lower level** than that of healthy cells and electrical connections are disrupted.

In writing this monograph I have come to the opinion that liquid crystal components of cells and the extracellular matrix of the body possess many of the features of electronic circuits. I believe that components analogous to conductors, semiconductors, resistors, transistors, capacitors, inductor coils, transducers, switches, generators and batteries exist in biological tissue

Examples of components that allow cells to function as solid-state electronic devices include: transducers (membrane receptors), inductors (membrane receptors and DNA), capacitors (cell and organelle membranes), resonators (membranes and DNA), tuning circuits (membrane-protein complexes), and semiconductors (liquid crystal protein polymers).

The major hypothesis of this monograph is that cancer cells have different electrical and metabolic properties due to abnormalities in structures outside of the nucleus. The recognition that cancer cells have different electrical properties leads to my hypothesis that therapies that address these electrical abnormalities may have some benefit in cancer treatment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089769/

Capacitance of Membrane As a Prognostic Indicator of Survival in Head and Neck Cancer 2016

The electrical properties of cancer cells are different than the electrical properties of the normal tissues that surround them. Cancer cells have higher intracellular sodium, lower intracellular potassium, magnesium and calcium concentrations, and more negative charges on their cell surface. These abnormalities result in cancer cells having lower transmembrane potentials and electrical impedance than normal cells and altered membrane permeability [2,3].

https://pubmed.ncbi.nlm.nih.gov/9001609/

Impedance spectra of tumour tissue in comparison with normal tissue; a possible clinical application for electrical impedance tomography 1996

Tumour tissue has been shown to exhibit a larger permittivity and conductivity than normal tissues. This might be associated with the fact that tumour cells have a higher water content and sodium concentration than normal cells, as well as different electrochemical properties of their cell membranes.

https://iopscience.iop.org/article/10.1088/0967-3334/30/5/003

Electrical conductivity measurement of excised human metastatic liver tumours before and after thermal ablation 2009

The average conductivity of tumour tissue was significantly higher than normal tissue over the entire frequency range (from 4.11 versus 0.75 mS cm^{-1} at 10 Hz, to 5.33 versus 2.88 mS cm^{-1} at 1 MHz).

https://pubmed.ncbi.nlm.nih.gov/12538062/

A review of electrical impedance techniques for breast cancer detection 2003

Some evidence has been found that malignant breast tumors have lower electrical impedance than surrounding normal tissues.

https://pubmed.ncbi.nlm.nih.gov/17664638/

A method for analyzing electrical impedance spectroscopy data from breast cancer patients 2007

Research on freshly-excised malignant breast tissues and surrounding normal tissues in an in vitro impedance cell has shown that breast tumors have different conductivity and permittivity from normal or non-malignant tissues. This contrast may provide a basis for breast cancer detection using electrical impedance imaging.

Plots of complex impedance showed shifts to higher impedance in some abnormal breasts, and generally greater variability among abnormal breasts.

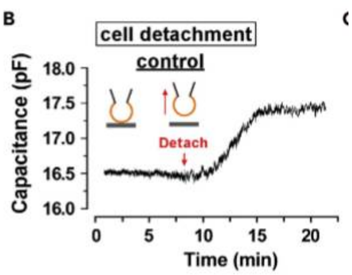
https://pubmed.ncbi.nlm.nih.gov/35936739/
Electrical Impedance Analysis for Lung Cancer: A Prospective, Multicenter, Blind Validation Study 2022
In total, 418 patients completed the entire protocol for clinical validation, with 186 true positives, 145 true negatives, 52 false positives, and 35 false negatives.

https://pubmed.ncbi.nlm.nih.gov/34888126/
Skin Electrical Resistance as a Diagnostic and Therapeutic Biomarker of Breast Cancer Measuring Lymphatic Regions 2021
Significant differences between malignant and benign breast lesions were obtained ($p<0.01$), also pre- and post-treatment ($p<0.05$). The diagnostic algorithm demonstrated the capability to classify breast cancer with an area under the curve of 0.68, sensitivity of 66.3%, specificity of 78.5%, positive predictive value 70.7% and negative predictive value 75.1%. Measurement of skin resistance in patients with breast cancer may serve as a convenient screening tool for breast cancer and evaluation of therapy. Further work is warranted to improve our approach and further investigate the biophysical mechanisms leading to the observed changes.

https://www.nature.com/articles/s42003-022-04077-2
Voltage imaging reveals the dynamic electrical signatures of human breast cancer cells 2022
Cancer cells feature a resting membrane potential (V_m) that is depolarized compared to normal cells, and express active ionic conductances, which factor directly in their pathophysiological behavior. Despite similarities to 'excitable' tissues, relatively little is known about cancer cell V_m dynamics. Here high-throughput, cellular-resolution V_m imaging reveals that V_m fluctuates dynamically in several breast cancer cell lines compared to non-cancerous MCF-10A cells.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/9781118687864.app3
Electrical Properties of Cells
Biological membranes have a
capacitance of approximately10^{-6} F (that is, 1 microfarad, or μF) per cm 2 of membrane area. From this value of membrane capacitance, the thickness of the insulating lipid portion of the membrane can be estimated using the following relation:
x= eo * k/C
In this equation, x is the distance between the conducting plates (that is, the ICF and the ECF), C is the capacitance of the plasma membrane (1 μF/cm 2), ε0
is the permittivity constant (8.85×10^{-8} μF/cm), and κ is the dielectric constant of the insulating material separating the two conducting plates (κ = 5 for membrane lipid). The calculated membrane thickness is approximately 4.5nm, which is similar to the membrane thickness of approximately 7.5 nm estimated with electron microscopy.

https://www.researchgate.net/publication/350932574_Survival_of_detached_cancer_cells_is_regulated_by_movement_of_intracellular_NaK-ATPase
Survival of detached cancer cells is regulated by movement of intracellular Na+,K+-ATPase 2021
Interestingly, the cell detachment significantly increased the membrane capacitance (Figures 5B and 5G)



https://www.researchgate.net/publication/324815806_Electrical_Characterization_of_Normal_and_Cancer_Cells
Electrical Characterization of Normal and Cancer Cells 2018
Empirically, normal cells were observed to exhibit higher dielectric constants when compared to cancer cells from the same tissue.
This shows that cancer cells of different cell origin possess their own signature electrical parameters, especially when compared to their normal counterparts
Therefore, a cancer cell is expected to have its own signature changes that are believed to affect its electrical properties. One of the earliest observations of such changes was the reduced transmembrane potential of cancer cells, which correlates well with their high mitotic activity [2]
Moreover, cancer cells also have disrupted cell membrane permeability that affects their intracellular ionic composition since compared to normal cells, cancer cells were found to have higher concentrations of sodium and chlorine [5] and less concentrations of potassium, calcium, zinc and magnesium, as well as a higher water content [6
Beside all the above, cancer cells are known to have a disturbed pH profile since their extracellular space is usually acidic, while the intracellular environment is alkaline, unlike normal cells [13].
Breast cells were found to have the highest capacitance value followed by liver and then lung cells (Fig. 2). This shows that cells from different tissue origins possess different electrical properties. Generally, and independent of cell type, normal cells exhibited higher capacitance values when compared to their cancer counterparts.

https://pubmed.ncbi.nlm.nih.gov/24663430/

Human oral cancer cells with increasing tumorigenic abilities exhibit higher effective membrane capacitance 2014
Conclusion: This is the first study showing that OSCC cells with higher tumour formation ability exhibit higher effective membrane capacitance than cells that are less tumorigenic.

https://pubmed.ncbi.nlm.nih.gov/35447510/
Direct investigations of the electrical conductivity of normal and cancer breast cells by conductive atomic force microscopy 2022
The processes of the normal breast cells also exhibit the capacitor behavior. While the processes of the breast cells are electrically conductive along micrometer length scales, and show the semiconductor like conductive characteristics with Schottky barrier of 0.8391 V. All these demonstrate that the electrical conductivity of the cancer breast cells is better than the normal breast cells. This work will be helpful in the further investigations of electrical conductivity of normal and cancer cells at nanometer level, and will also pave new way in the distinguishing the cancer cells and tissues from the normal cells and tissues.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6752768/
Characterization of sequentially-staged cancer cells using electrorotation 2019
The electrical properties of malignant cells, including the membrane capacitance and cytoplasmic conductivity, have been demonstrated to be altered compared to non-malignant cells of similar origin. Here, we exploit these changes to characterize individual cells in a sequentially-staged *in vitro* cancer model using electrorotation (EROT)—the rotation of a cell induced by a rotating electric field.
Our results also indicate that membrane capacitance, membrane conductance, and cytoplasmic conductivity increase with an increasingly malignant phenotype.