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MINI REVIEW **OPEN ACCESS**

Membrane Potential Inhibitors and Their Paradoxical Role in Cancer Development and Progression: A review

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ABSTRACT

The membrane potential (Vm) is a basic biophysical feature of cells that is controlled by the coordinated work of ion channels, pumps, and transporters. There is more and more proof that changes in Vm are directly related to cell growth, differentiation, and death. Compared to normal cells, cancer cells usually have a depolarised membrane potential. This is linked to their ability to grow and spread more quickly. Ion channel inhibitors have shown potential as therapeutic drugs in oncology; nonetheless, there is increasing apprehension that non-specific or extended suppression of membrane potential-regulating systems may inadvertently facilitate tumour genesis and progression. This review critically analyses the dualistic function of membrane potential inhibitors in cancer biology, emphasising the pathways by which dysregulated bioelectric signalling may facilitate oncogenesis, alongside the circumstances in which targeted inhibition may confer therapeutic advantages. To safely and effectively use bioelectric targets in cancer treatment, you need to understand this balance.

Key words*: Ion channels, cancer progression, depolarisation, calcium signalling, bioelectricity, oncogenesis, and ion channel inhibitors are some of the most important terms. Beginning*

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INTRODUCTION

Cancer continues to be a primary cause of illness and mortality globally, resulting from a complex interaction of hereditary, epigenetic, and environmental variables. In recent years, there has been a growing interest in the function of bioelectric signalling in cancer biology. One of the most important parts of this system is the membrane potential (Vm), which is the electrical gradient that forms across the plasma membrane of cells [1]. This electrochemical feature is essential for maintaining cellular homeostasis, affecting processes like proliferation, differentiation, apoptosis, and communication between cells. Membrane potential was not given much thought in the past, but it is now known to be an important factor in how tumours behave.

In normal somatic cells, the membrane potential is usually kept in a condition of hyperpolarisation, which helps the cells stay quiet and do their jobs. In contrast, cancer cells frequently demonstrate a consistently depolarised membrane potential. This change in electrical state is not just a result of cancerous change; it also helps it happen [2]. Depolarisation has been linked to accelerated cell cycle progression, apoptosis resistance, metabolic reprogramming, and heightened metastatic potential. Consequently, the bioelectric profile of a cell can function as both a biomarker and a catalyst for oncogenesis [3]. Ion channels, pumps, and exchangers carefully control the passage of ions across the plasma membrane. These ions are mainly potassium (K^+), sodium (Na^+), calcium (Ca^{2+}), and chloride (Cl^-). This movement creates and keeps the membrane potential. These ionic gradients are necessary for many bodily activities. For example, the membrane potential governs calcium signalling inside cells, which in turn controls gene expression, enzyme activity, and the movement of the cytoskeleton. It also helps keep cellular metabolism going and coordinates how cells respond to things outside of them. During the cell cycle, it is important for the membrane potential to alter in a dynamic way. Hyperpolarisation is usually linked to the movement from quiescence to DNA synthesis, whereas depolarisation helps mitosis move forward [4]. However, cancer cells have unique bioelectric fingerprints that make them different from normal cells. These consist of prolonged depolarisation, abnormal expression or functionality of ion channels, and heightened intracellular calcium oscillations. These changes turn on carcinogenic signalling pathways, speed up DNA synthesis, and make cells resistant to programmed cell death. The idea that cancer is a "bioelectric disorder" has become more popular, leading to the new area of cancer electrophysiology [5]. Interestingly,

ion channel inhibitors, which are often used to treat heart, brain, and metabolic problems, have been looked into for their possible anticancer effects. These substances can change the membrane potential and mess up the ionic environment that tumours need to thrive. A paradox has arisen: targeted blocking of specific ion channels may impede tumour progression, yet non-specific or protracted disruption of membrane potential regulation can, in certain circumstances, facilitate carcinogenesis. One reason for this contradiction is because regular cell cycle control is messed up. The cell cycle moves forward thanks to very small changes in membrane potential. Non-specific blocking of ion channels may disrupt these oscillations, resulting in dysregulated cell division and uncontrolled proliferation. Instead of stopping the growth of tumours, this kind of disruption may make things worse by making them more likely to become cancerous [6].

Changing the way calcium signals work is another important part of this process. Voltage-gated calcium channels let calcium in through the membrane potential. Calcium ions function as ubiquitous second messengers, modulating gene transcription, cellular survival pathways, and apoptosis. When the membrane potential is disturbed, calcium may flow in abnormally, which might activate cancer-causing pathways including MAPK and PI3K/Akt. Calcium signalling that lasts a long time can help cells live and grow instead of dying [7].

Some membrane potential inhibitors may also cause or keep a chronically depolarised state, which is similar to the electrical phenotype of cancer cells. This pro-depolarized environment encourages the start of tumours, increases the "stemness" of cells, and encourages dedifferentiation. Cells in this condition are more likely to develop malignant traits, such as enhanced proliferative ability and resistance to regulatory signals [8].

Ion channels are also very important for controlling how the cytoskeleton is organised, how cells stick together, and how they move. Their dysregulation can increase the likelihood of metastasis by encouraging processes like epithelial–mesenchymal transition (EMT). Using these methods, cancer cells can infect nearby tissues and form secondary tumours in other parts of the body. So, changing the activity of ion channels in the wrong way may help cancer spread instead of stopping it.

Some membrane potential inhibitors can also affect how mitochondria work, in addition to these effects. When the mitochondrial membrane potential is disrupted, it can cause more reactive oxygen species (ROS) to be generated. This can lead to oxidative stress, DNA damage, and genomic instability. While sudden spikes in ROS can cause apoptosis, long-term oxidative stress is a well-known cause of cancer, which shows that these treatments have both positive and negative effects [9].

Even though there are some hazards, membrane potential inhibitors are still viable weapons for treating cancer when used correctly. Potassium channel blockers, for instance, have been demonstrated to cause apoptosis, reduce tumour proliferation, and obstruct angiogenesis. Sodium channel inhibitors can make cancer cells less likely to spread and limit the spread of cancer to other parts of the body, especially in tumours that are very aggressive. Calcium channel modulators have also been shown to stop cell division and slow down the growth of cells [10].

Specificity is the key to making the most of the therapeutic potential of these medicines. Future techniques should concentrate on selectively targeting ion channels that are particularly expressed or hyperactive in cancer cells, while preserving normal tissues. Combining ion channel modification with standard chemotherapy, targeted therapy, or immunotherapy may make treatments work better. Also, progress in personalised medicine, such bioelectric profiling of tumours, could make it possible to make therapies that are specific to the unique electrophysiological traits of each patient [11].

There are still a number of problems, though. Many ion channel inhibitors that are now on the market don't work very well and can have side effects that make cells not work properly. We still don't fully understand how bioelectric signalling networks work, and when we want to use experimental results in real life, we need to be very careful about dosage, timing, and delivery methods. To safely and effectively add bioelectric therapies to cancer treatment, these problems must be solved [12].

The field of cancer electrophysiology has tremendous chances for new ideas in the future. Finding bioelectric biomarkers could help find and diagnose cancer earlier. The creation of very selective ion channel modulators could lead to novel treatments with fewer adverse effects. In addition, combining electrophysiological methods with molecular and genomic studies could provide us a better picture of how cancer works. Bioelectric modulation may have uses in cancer prevention and regenerative medicine in addition to treatment [13].

CONCLUSION

Membrane potential is a key factor that controls how cells act, and when it goes wrong, cancer is a sign of it. Membrane potential inhibitors have a lot of promise as cancer-fighting drugs, but their effects depend a lot on the situation. Non-specific or persistent inhibition can interfere with normal bioelectric signalling

and may facilitate cancer development and progression. Consequently, a more profound comprehension of the complex interactions among ion channels, membrane potential, and carcinogenic pathways is needed. This information will help us come up with better and more accurate ways to treat cancer, getting the most benefits while lowering the risks.

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