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Editorial

Use of nanosecond pulsed electric fields in brain tumors

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Nanosecond pulsed electric fields (nsPEFs) are a recently discovered technology where intense electric pulses are used to treat tumors. They penetrate intracellular organelles without causing much damage to the plasma membrane. The major mechanism of action is through inducing mitochondrial-dependent apoptosis. This treatment method has been used in malignancies such as melanoma but not widely in the treatment of CNS tumors. The use of this promising technology in the treatment of CNS tumors may offer new hope for patients afflicted with these conditions.

The use of nsPEFs in medicine has been a subject of considerable interest since the early 2000s, especially in the field of oncology. nsPEFs are very intense electric pulses in the nanosecond (ns) domain (ranging from 3 to 600 ns). Furthermore, other forms of electric pulses include those in the millisecond (ms), microsecond (μs), and picosecond (ps) domain.

There are two unique properties of nsPEFs that distinguish them from pulses in the other domains: their effects in penetration to intracellular organelles and the large electric field amplitude. Unlike conventional electroporation methods, they target intracellular organelles without causing much damage to the plasma membrane, only forming ≈1 nm pores there. It has been found that the basic mechanism of apoptosis through nsPEFs is mitochondrial-dependent caspase activation, confirmed by the presence of cytochrome c after the application of nsPEFs to cultured cells.[2] Many studies have reported apoptosis among cells after the application of high-intensity (>100 kV/cm) nsPEFs. However, even moderate-intensity nsPEFs (10–80 kV/cm) can cause cells to undergo apoptosis. This property makes nsPEFs, particularly feasible for inducing tumor regression.

It is also found that nsPEFs have a profound effect on causing an antitumor response in experimental mice.[8] This response involved an increase in the production of T-cells, especially $CD8^+$ cells, leading to a rise in the $CD8^+$/CD3 ratio. Macrophage and dendritic cells were found to increase post application while immunosuppressive myeloid cells were found to decrease. An important discovery was the increase in TNF-α and IL-1β, both of which are pro-inflammatory cytokines, affecting the local and systemic responses. In addition, treatment by nsPEFs significantly inhibited IL-6 secretion and downregulated IL-6 expression. This has the effect of limiting immune suppressive cells such as myeloid-derived suppressive cells (MDSCs) and T-regulatory cells (Tregs).

nsPEFs have previously been used in superficial malignancies as well as tumors including but not limited to melanoma, hepatocellular carcinoma, pancreatic cancer, basal cell carcinoma, cutaneous papilloma, squamous cell carcinoma, kidney cancer, and prostate cancer.[3,7] Various

animals such as pigs, rats, and dogs have been used for experimental studies. For instance, in hepatocellular carcinoma in mice, nsPEF ablation not only induced cell death of hepatic cancer cells but also reduced pulmonary metastasis of the carcinoma. It, further, enhanced phagocytosis by macrophage cells and even suppressed tumor growth in human tissue implanted in the mouse.[7]

Microsecond pulsed electric fields have been able to induce irreversible membrane permeabilization and apoptosis, and reactive oxygen species (ROS) production, resulting in tumor volume reduction in medulloblastoma cancer stem cells.[6] The tumor mass, however, remained the same. According to one study,[4] though nsPEFs were unable to cause ROS production or apoptosis, they have been able to cause transcriptional changes such as a change in cell morphology and cell fusion. Therefore, therapeutic applications exist. Nanosecond pulses generated by metal-oxide-semiconductor field-effect transistors (MOSFETs) have also achieved well-controlled electrical manipulation in the D283 cell line *in vitro*.[5] MOSFETs may be useful due to their ability to alter pulse width, frequency, and amplitude.[5]

Although the clinical use of nsPEFs in CNS tumors has been limited, they are promising in cancer treatment as they show several advantages over conventional surgical resection, electrochemotherapy, and invasive techniques. Being minimally invasive, drug-free, and nonthermogenetic, nsPEFs can certainly be an asset in the treatment of brain tumors. Furthermore, it is shown that nsPEFs can cause apoptosis without the entry of calcium (Ca^{2+}) and are effective in intracellular penetration so, therefore, have wide applications in causing regression of tumor cell lines. Since nsPEFs cause disruption of vascularization of these tumor cells, it can cause regression of growth by necrosis as well.[3]

According to a report by Bardet *et al*.,[1] multiphoton imaging was used to assess the impact of nsPEFs applied on a tumor organoid model of glioblastomas. The results were promising as a single 10 ns, high-voltage electric impulse (35–45 kV/cm) slightly altered vessel diameter in normal tissues but completely collapsed the perfusion of neurovasculature in tumor tissue. The response was the highest in small disorder vessels such as those found in tumors, rendering larger thick-walled arteries unaffected. This confirms the potential use of nsPEFs in brain tumors owed to their ability to cause disruption.

Cancer remains a major cause of mortality all around the globe despite consistent efforts of the scientific community to find the best possible solution. Although CNS tumors may not be eliminated by nsPEFs in absolute terms, any ray of hope is worth considering and trying for.

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